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# CONTENTS OF VOLUME 44

JULY, 1929 NUMBER 1

	PAGE
Opium Addiction VI The Effects of Abrupt Withdrawal Followed by Readministration of Morphine in Human Addicts, with Special Reference to the Composition of the Blood, the Circulation and the Metabolism Arthur B Light, M D, and Edward G Torrance, M D, Philadelphia	1
The Regulation of Blood Sugar in Idiopathic Steatorrhea (Sprue and Gee-Herter's Disease) I The Low Blood Sugar Curve T E Hess Thaysen, M D, and A Norgaard, M D, Copenhagen, Denmark	17
Further Observations on the Contour of Normal and of Tuberculous Chests S A Weisman, M D, Minneapolis	29
Sugar Tolerance in Arthritis I Chronic Infectious Arthritis Benjamin H Archer, M D, New York	37
Fructosuria P A Heeres, M D, and Herman Vos, M D, Groningen, Holland	47
Hyperinsulinism Report of Two Cases Frank N Allan, M D, Rochester, Minn	65
An Improved Duodenal Tube Its Advantages, with a Brief Outline of Duodenal Intubation C Victor Richards, M D, Baltimore	71
Toxic Adenoma of Thyroid Solomon Ginsburg, M D, New York	73
The Effect of the Purine Base Diuretics on the Coronary Flow N C Gilbert, M D, and G K Fenn, M D, Chicago	118
Undulant Fever Presenting the Clinical Syndrome of Intermittent Hydrarthrosis B M Baker, Jr, M D, Baltimore	128
The Pathologic Aspect of Some Epilepsies Alfred Gordon, M D, Philadelphia	142
Motility of the Rectum in Normal and in Constipated Subjects L E Hines, M D, H C Lueth, M S, and A C Ivy, M D, Chicago	147
Book Reviews	153

AUGUST, 1929 NUMBER 2

Diseases of the Liver VIII The Various Types of Syphilis of the Liver with Reference to Tests for Hepatic Function Paul A O'Leary, M D, Carl H Greene, M D, and Leonard G Rowntree, M D, Rochester, Minn	155
Opium Addiction VII A Comprehensive Study of Effects of the Scopolamine Treatment for Morphine Addiction Arthur B Light, M D, and Edward G Torrance, M D, Philadelphia	194
Blueberry Leaf Extract Overdosage Leonard Benjamin Shpiner, B S, Chicago	204
The Reticulocyte Count in Normal and in Abnormal Conditions Alfred Friedlander, M D, and Charlotte Wiedemei, M D, Cincinnati	209
The Variability of Blood Pressure II A Study of Systolic Pressure at Five Minute Intervals H S Diehl, M D, and H D Lees, M D (Tor), Minneapolis	229
Sugar Tolerance in Arthritis II Arthritis of the Menopause Benjamin H Archer, M D, New York	238
Inorganic Serum Sulphates in Renal Insufficiency A Comparative Study of Blood Urea and Creatinine, the Effect of Diuresis on Serum Sulphates E G Wakefield, M D, Rochester, Minn	244
A Chemical Study of Urine as Effected by Combinations of Ammonium Chloride and Methenamine Edwin C Wise, M S, and Frederick W Hevl, Ph D, Kalamazoo, Mich	252

# CONTENTS OF VOLUME 44

## AUGUST—Continued

	PAGE
The Relation of Withdrawal of Cerebrospinal Fluid to the Body Temperature Consideration of a Thermoregulatory Center, a Study of Two Hundred and Fifty Cases Alfred Gordon, M D, Philadelphia	263
Thrombo-Angioneurotic Changes of the Kidneys in Chronic Nephritis Bernard Sternberg, M D, Brooklyn	272
Toxic Cirrhosis of Liver Due to Cinchophen Herbert S Reichle, M D, Cleveland	281
The Pneumotachograph in Certain Intrathoracic Diseases Its Diagnostic Value Max Hochrein, M D, and Soma Weiss, M D, Boston	289
Book Reviews	301

## SEPTEMBER, 1929 NUMBER 3

The Treatment of Pyuria Due to Bacillus Coli A Hecht Johansen, M D, Boston	303
Benign Gastric and Duodenal Ulcers Clinical Diagnosis and the Conditions Found at Operation Howard R Hartman, M D, and Andrew B Rivers, M D, Rochester, Minn	314
The Pituitary Gland and the Suprarenal Cortex Robert C Moehlig, M D, Detroit	339
The Effect of Uncooked Starches on the Blood Sugar of Normal and of Diabetic Subjects II Sanford M Rosenthal, M D, and Edwin E Ziegler, M D, Washington, D C	344
The Amino-Acid Content of the Blood in Health and in Disease E G Schmidt, Ph D, Baltimore	351
Failure of a Diabetic Patient to Utilize Dried Artichoke Powder L E Westcott, M D, and E C Wise, M S, Kalamazoo, Mich	362
The Cerebrospinal Fluid in Myxedema Willard Owen Thompson, M D, Phebe K Thompson, M D, Esther Silveus, A B, and Mary Elizabeth Dailey, A B, Boston	368
The Diuretic Action of the Parathyroid Extract W C Hueper, M D, Chicago	374
Opium Addiction VIII The Effects of Intramuscular and Intravenous Administration of Large Doses of Morphine to Human Addicts Arthur B Light, M D, and Edward G Torrance, M D, Philadelphia	376
The Arterioles in Cases of Hypertension James W Kernohan, M B, Edward W Anderson, M D, and Norman M Keith, M D, Rochester, Minn	395
Prolongation of the Life of Nephrectomized Dogs with the Production of Edema E E Lyon, M S, A L Shafton, M S, and A C Ivy, M D, with the Assistance of F S Barry, Chicago	424
The Action of Merbaphen (Novasurol) on the Kidney of the Dog A Com- bined Functional and Pathologic Study Harrow M Keith, M B, and B I Johnstone, M B, Detroit	438
Secretion of Bile in Response to Rectal Instillations Abraham Leon Garbat, M D, and Harry George Jacobi, M D, New York	455
Book Reviews	463

## OCTOBER, 1929 NUMBER 4

Edema in Congestive Heart Failure Effectiveness of Diuretics as a Guide to Prognosis William Goldring, M D, New York	465
Blood Sugar Regulation in Idiopathic Steatorrhea II The Origin of the Low Blood Sugar Curve T E Hess Thaysen, Copenhagen, Denmark	477

OCTOBER—Continued

	PAGE
Renal Insufficiency Associated with Bence-Jones Proteinuria Report of Thirteen Cases with a Note on the Changes in the Serum Proteins Edwin G Bannick, M D, and Carl H Greene, M D, Rochester, Minn	486
Reticulocytosis Produced by Liver Extract Two, Three and Four Hour Interval Observations William B Porter, M D, and Hazelwood Irving, Richmond, Va	502
The Hemoglobin Percentage and the Red Blood Cell Count in Bright's Disease, Myocardial Insufficiency and Hypertension Benjamin Ashe, M D, New York	506
The Effect of Sodium Chloride on Hypertension Samuel S Berger, M D, and M H Fineberg, M D, Cleveland	531
Intestinal Obstruction and Septic Invasion of the Peritoneum Combined Medical and Surgical Treatment Kenneth Phillips, M D, and W Parker Stowe, M D, Miami, Fla	543
Effects of Diathermy Treatments on Temperature Wilhelm Stenstrom, Ph D, and Paul Nurnberger, A B, Minneapolis	556
Meningo-Encephalitis Due to Torula Histolytica Willard J Stone, M D, and B F Sturdivant, M D, Pasadena, Calif	560
Diabetes Mellitus Pathologic Changes in the Spinal Cord and Peripheral Nerves Henry W Woltman, M D, and Russell M Wilder, M D, Rochester, Minn	576
Massive Pulmonary Atelectasis (Collapse) Its Probable Mechanism and Clinical Significance Herman Hennell, M D, New York	604
Book Reviews	621

NOVEMBER, 1929 NUMBER 5

Constitutional Variation and Susceptibility to Disease Wade H Brown, M D, New York	625
The Pathology of the Pancreas in Nondiabetic Persons A Study of One Hundred and Fifty-Six Consecutive Autopsies on Nondiabetic Patients Shields Warren, M D, Boston	663
Calcium Studies A Cantarow, M D, Philadelphia	
IV The Calcium Content of Cerebrospinal Fluid	667
V The Relationship Between the Calcium Content of Cerebrospinal Fluid and Blood Serum	670
The Effect of Mechanical Constriction of the Hepatic Veins, with Special Reference to the Coagulation of Blood W W Brandes, M D, Chicago	676
Opium Addiction IX Water Balance Studies During the Administration and the Withdrawal of Morphine Arthur B Light, M D, and Edward G Torrance, M D, Philadelphia	693
Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma Walter H Nadler, M D, and John A Wolfer, M D, Chicago	700
Tuberculosis of the Aorta Report of a Case Leyland J Adams, M D, Montreal, Canada	711
Boeck's Sarcoid Report of a Case with Visceral Involvement Mitchell Bernstein, M D, Frank W Konzelmann, M D, and D M Sidlick, M D, Philadelphia	721
Malignant Lesions of the Gallbladder E Starr Judd, M D, and Conrad J Baumgartner, M D, Rochester, Minn	735
Carcinoma of the Renal Cortex with Factors Bearing on Prognosis E Starr Judd, M D, and John R Hand, M D, Rochester, Minn	746
Eosinophilic Hyperleukocytosis in Hodgkin's Disease with Familial Eosinophilic Diathesis Report of a Case and Review of the Literature Sloan G Stewart, M D, Philadelphia	772
Book Reviews	784

Rate of Evacuation of Various Foods from the Normal Stomach A Preliminary Communication Malcolm J Wilson, M D , W H Dickson, M D, and A C Singleton, M D, Toronto, Canada	787
Blood Pressure in Diabetes Mellitus A Statistical Study S G Major, M D, Minneapolis	797
The Rate of Glycolysis in Erythremia (Polycythemia Vera) Jerome E Cook, M D, and Michael Somogyi, Ph D, St Louis	813
The Bromsulphalein Hepatic Function Test Report of a Series of Tests V H Cornell, M D, San Francisco	818
Calcium Studies VI The Effect of Parathyroid Extract on the Diffusibility of Calcium in Human Beings A Cantarow, M D, Philadelphia	834
The Systolic Blood Pressure in Duodenal and Gastric Ulcer A Statistical Study Howard R Hartman, M D, and George E Brown, M D, Rochester, Minn	843
Influence of the Diaphragm on the Esophagus and on the Stomach Minas Joannides, M D, Chicago	856
Opium Addiction	
X The Excretion of Morphine by Human Addicts Edith G Fry, A B , Arthur B Light, M D , Edward G Torrance, M D, and William A Wolff, A M, Philadelphia	862
XI General Summary Arthur B Light, M D, Philadelphia	870
Blood Pressure and Weight Howard R Hartman, M D, and David G Ghrist, M D, Rochester, Minn	877
Hemochromatosis in a Metal Worker Case Report with Autopsy and a Brief Review of the Literature F C Wood, M D, and T Fitz-Hugh, Jr, M D, Philadelphia	882
Experimental Left and Right Axis Deviation Clayton J Lundy, M D, and Lewis W Woodruff, M D, Chicago	893
Book Reviews	908
General Index	911

## OPIUM ADDICTION

VI THE EFFECTS OF ABRUPT WITHDRAWAL FOLLOWED BY READMINISTRATION OF MORPHINE IN HUMAN ADDICTS, WITH SPECIAL REFERENCE TO THE COMPOSITION OF THE BLOOD, THE CIRCULATION AND THE METABOLISM \*

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AND

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Continuing our studies on a series of male opium addicts, we wish to report the results obtained when the morphine administered to supply the patients' needs was abruptly withdrawn. These results include studies made at three hour intervals for a twenty-four hour period following the last administration of morphine and another series of results obtained when the drug had been stopped for forty-eight hours. Following the studies at the close of the forty-eight hour period, morphine was again administered to allay all suffering and again the same observations and studies were made.

### EXPERIMENTAL PROCEDURE

Two separate methods of approach were used in the study of changes brought about by the abrupt withdrawal of morphine which was being administered to supply the addict's need. One group was studied at intervals of three hours following the last administration of the drug, in four cases the studies were carried over a period of twenty-four hours. Another group of ten patients was studied immediately following the administration of the regular scheduled dosage, and the studies were then discontinued except for observations on the behavior until the end of a forty-eight hour withdrawal period, when the same studies were again made just before and after morphine was given again to allay all symptoms.

Only four of the eight patients selected in the first group were studied over periods of three hour intervals for twenty-four hours.

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\* Submitted for publication, March 5, 1929

\* From the Narcotic Wards of the Philadelphia General Hospital

<sup>1</sup> Expenses of this research were defrayed by the Committee on Drug Addictions, New York City, and were carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction, in the wards of the Philadelphia General Hospital which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia

The behavior and cooperation of the others were not conducive to accurate observations. No food was given during this period. The addicts were always required to remain in bed for a period of one-half hour before any studies were made.

Figures showing the pulse and respiration rates are the average of a five minute count. The figures for the blood pressure were obtained from as many patients as it was possible to measure the blood pressure of accurately within a five minute period, followed by a record of temperatures taken both by mouth and by rectum. When these observations were finished the basal metabolic rate was determined with Krogh's apparatus for recording basal metabolism, following which a sample of blood was drawn from a vein at the elbow. At the end of each period, the subject passed a sample of urine.

The procedure in the study of the group in which the drug was abruptly withdrawn for a period of forty-eight hours was quite similar. Following the administration of the last regular scheduled amount of morphine in the morning, the subjects immediately reclined in bed without breakfast and observations were made on circulation and respiration, and a sample of blood was taken after a rest period of half an hour. The subjects then resumed the standing position for a period of five minutes, and observations were made. A sample of blood was taken for analysis, and following this the addicts were subjected to the staircase climbing test which we have described in detail in another paper.<sup>1</sup> Except for observations concerning their conduct and remarks, further studies were not made until the completion of the withdrawal period. Food was allowed during the first thirty-six hours of this period, but in no cases was any taken at the expiration of the first twenty-four hours. At the end of the withdrawal period the addicts were again requested to recline, and the same observations were conducted. Blood was drawn and the staircase climbing tests were again carried out.

With the completion of these observations and studies, the addicts were given sufficient morphine to supply their needs. As soon as they professed to feel normal the same studies, including the drawing of the blood and the staircase climbing tests, were again carried out.

## RESULTS

In table 1 we have tabulated the highest, lowest and average figures of the determinations and observations, together with the number of cases studied at three hour intervals for a period of twenty-four hours following the abrupt withdrawal of morphine. The word "basal" in the table indicates the results obtained immediately following the last injection.

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1 Light, A. B., and Torrance, E. G. *Opium Addiction. III. The Circulation and Respiration of Human Addicts During the Administration of Morphine*, *Arch. Int. Med.* **43**: 556 (April) 1929.

TABLE 1—*Studies of Human Opium Addicts at Three Hour Intervals for a Period of Twenty-Four Hours Following the Withdrawal of Morphine*

		Basal	3d Hour	6th Hour	9th Hour	12th Hour	15th Hour	18th Hour	21st Hour	24th Hour
Pulse	No cases	8	8	8	5	5	5	4	4	4
	Highest	80	76	78	76	74	73	75	78	80
	Lowest	58	57	53	51	55	63	60	57	67
	Average	68	62	64	68	64	66	69	70	74
Blood pressure while reclining	No cases	8	8	8	5	5	5	4	4	4
	Highest	125/84	119/79	120/84	130/78	130/85	135/82	118/71	112/69	118/72
	Lowest	103/65	105/60	103/61	107/60	104/61	108/63	104/59	101/58	106/66
	Average	116/74	114/70	114/71	116/69	112/70	118/71	110/67	107/65	112/69
Respira- tions	No cases	8	9	8	5	5	5	4	4	4
	Highest	18	15	15	23	22	18	16	16	15
	Lowest	11	11	10	12	11	12	9	9	10
	Average	14	13	13	17	15	15	13	12	13
Tempera- ture by mouth	No cases	8	8	8	5	5	5	4	4	4
	Highest	98.8	98.7	98.7	99.0	99.1	99.4	99.0	99.6	101.1
	Lowest	97.3	97.6	97.2	98.1	98.4	98.5	98.6	98.8	99.2
	Average	98.4	98.4	98.2	98.5	98.6	98.9	98.8	99.0	99.7
Rectal tempera- ture	No cases	8	8	8	5	5	5	4	4	4
	Highest	99.6	99.4	99.7	99.6	99.7	99.8	99.9	100.6	101.9
	Lowest	98.0	98.7	98.0	98.7	98.9	98.8	99.4	99.6	99.9
	Average	99.2	99.1	99.2	99.2	99.4	99.3	99.6	100.0	100.7
Hemo- globin	No cases	8	8	6	3	4	4	4	4	4
	Highest	19.8	19.1	20.3	15.9	16.1	16.5	18.6	18.2	17.9
	Lowest	14.1	10.8	13.2	9.3	12.9	11.2	15.6	12.6	16.2
	Average	15.8	15.5	16.2	12.3	14.6	14.6	17.2	15.9	17.3
Erythro- cytes	No cases	8	8	7	5	3	5	4	4	4
	Highest	4,940	5,000	5,680	4,865	4,740	4,870	5,010	5,360	5,050
	Lowest	3,850	3,910	3,850	3,910	4,530	4,600	4,280	4,240	4,100
	Average	4,527	4,506	4,517	4,521	4,490	4,718	4,547	4,747	4,515
Leukocytes	No cases	8	8	7	5	3	5	4	4	4
	Highest	15,400	14,600	15,600	9,400	8,800	11,200	11,400	11,500	12,900
	Lowest	4,000	5,600	7,800	7,300	7,000	7,200	10,400	10,400	9,000
	Average	8,980	9,888	10,771	8,020	7,800	9,700	10,925	10,825	11,125
Polymor- phonu- clears	No cases	8	8	8	4	3	5	4	4	4
	Highest	77	79	74	66	59	69	73	76	77
	Lowest	48	48	51	46	53	55	67	65	72
	Average	61	61	61	58	57	63	69	70	75
Lympho- cytes	No cases	8	8	8	4	3	5	4	4	4
	Highest	46	44	43	42	41	39	27	30	24
	Lowest	19	18	19	28	34	21	23	19	18
	Average	33	33	33	34	36	30	25	24	20
Large mono- nuclears	No cases	8	8	8	4	3	5	4	4	4
	Highest	6	6	8	9	6	6	5	7	5
	Lowest	2	3	1	5	3	3	4	3	4
	Average	4½	4	4½	6	4	5	5	5	4½
Eosino- phils	No cases	8	8	8	4	3	5	4	4	4
	Highest	3	5	4	6	3	2	2	2	1
	Lowest	0	0	0	0	2	1	0	0	0
	Average	1	2	1	2	2	1	1	1	½
Basophils	No cases	8	0	8	0	3	0	0	0	0
	Highest	2	0	1	0	2	0	0	0	0
	Lowest	1	0	0	0	0	0	0	0	0
	Average	½	0	½	0	1	0	0	0	0
Urea	No cases	4	4	4	2	2	2	4	4	4
	Highest	12	13	13	10	10	10	15	13	17
	Lowest	8	8	9	10	9	8	10	10	9
	Average	10	10	11	10	9.5	9	11.5	11	11.5
Sugar	No cases	8	8	8	4	4	4	4	4	4
	Highest	107	111	113	107	93	100	107	111	109
	Lowest	60	83	78	63	69	76	80	89	100
	Average	86	94	91	84	81	86	91	100	105
Creatinine	No cases	4	1	4	2	2	2	4	4	4
	Highest	1.25	1.31	1.2	1.19	1.08	1.2	1.55	1.58	1.5
	Lowest	1.085	1.145	1.11	1.05	1.07	1.18	1.03	1.07	1.08
	Average	1.145	1.24	1.17	1.08	1.075	1.19	1.28	1.32	1.28



TABLE 1—*Studies of Human Opium Addicts at Three Hour Intervals for a Period of Twenty-Four Hours Following the Withdrawal of Morphine—Continued*

		Basal	3d Hour	6th Hour	9th Hour	12th Hour	15th Hour	18th Hour	21st Hour	24th Hour
Calcium	No cases	4	4	4	2	2	2	4	3	4
	Highest	10 46	10 97	10 82	10 50	10 8	10 4	10 48	10 38	11 63
	Lowest	9 84	9 23	9 12	9 03	9 45	9 63	9 99	6 53	9 90
	Average	10 15	10 22	9 99	9 76	10 12	10 01	10 19	8 47	10 72
Magnesium	No cases	2	2					3	3	3
	Highest	2 12	2 08					1 84	1 98	1 80
	Lowest	2 06	2 0					1 64	1 46	1 50
	Average	2 09	2 04					1 75	1 64	1 61
Specific gravity— plasma	No cases	8	6	8	4	3	4	4	3	4
	Highest	1 0282	1 0277	1 0296	1 0287	1 0281	1 0284	1 0283	1 0287	1 02931
	Lowest	1 0238	1 0238	1 0238	1 0239	1 0243	1 0239	1 0247	1 0249	1 02576
	Average	1 0261	1 0256	1 0263	1 0263	1 0257	1 0264	1 0261	1 0262	1 02687
Protein, per cent	No cases	8	7	8	4	3	4	4	4	4
	Highest	8 32	9	9 23	8 66	8 31	8 66	8 25	8 60	8 77
	Lowest	6 91	6	6 57	6 51	6 62	6 57	7 09	7 03	7 03
	Average	7 81	7 65	7 86	7 85	7 58	7 88	7 65	7 80	7 94
Conduc- tivity	No cases	8	7	8	4	3	4	4	4	4
	Highest	143	148	139 2	139	137 6	137 2	147 0	144 4	147 0
	Lowest	130	133	133 6	136	133 0	135 0	142 6	138 4	140 2
	Average	136 1	137 6	135 4	137 2	135 4	136 0	144 1	142 4	143 3
Basal metabolism	No cases	6	6	6	4	3	3	4	4	4
	Highest	20	14	19	11	6	24	14	14	36
	Lowest	-6	-12	2	6	-1	8	-9	-9	12
	Average	6	2	8	8	2	14	5	5	22

There was a slight average rise in the pulse rate and a slight fall in the systolic pressure. The average red blood cell count remained practically the same with a slight increase in the hemoglobin. A slight average increase in the white cells appeared, with a relative increase of polymorphonuclear cells and a decrease in the lymphocytes. Physical and chemical studies of the blood did not reveal any significant changes except for a slight fall in two cases in which the amount of magnesium present was determined and a slight rise in the conductivity of the serum found. A slight rise in the temperatures both by mouth and by rectum was noted. The average figure for basal metabolism shows a definite increase from +6 to +22. The cooperation of the patients, however, at the end of the twenty-four hour period was obviously not as good as when determinations were made following the last administration of the drug. Chemical and microscopic examination of the urine in the cases in which the drug was abruptly withdrawn failed to reveal the appearance of albumin or casts as well as any other positive signs. It was noted that the color of the blood drawn from the same vein without stasis in the same persons at three hour intervals varied considerably. If the addict complained of feeling hot, the blood flowing into the collecting tube was bright red, suggesting a high percentage saturation of oxygen. On the other hand if the addict complained of feeling chilly at the time, the blood was much darker in color, leading one to the belief that there existed a low percentage saturation of oxygen.

The physical changes noted in the addicts as the studies were carried on varied considerably. In the four cases in which the proposed twenty-four hour period of withdrawal was carried to completion the patients gave the observers the impression that they were suffering with a common cold in the head, lacrimation, sneezing and difficulty in breathing through the nostrils. Yawning was also present in these four cases, although it was not frequent. Dilatation of the pupils began between the sixth and ninth hour interval, in all cases. The patients complained of chills and exhibited the characteristic pilomotor activity of the skin known as "cold turkey" at the end of eighteen hours. Four showed slight muscular twitchings at the end of sixteen hours. None of the patients vomited, although at the end of the twenty-four hour period two complained of a serious gnawing sensation in the stomach which they interpreted as the need for the drug. Three addicts had a bowel movement at the end of the eighteen hour period without the aid of medication, something unusual with them while taking drugs at regular intervals. At the end of the twenty-four hours, two of the addicts showed a decided change in disposition, becoming extremely surly and repeatedly stating that they hoped we would stop our "foolishness" and give them their drug. At the end of eighteen hours, one patient was seized with a spell of laughter sufficient to produce severe lacrimation. He expressed his condition as a "laughing yen."

The results obtained during comparative studies following the last administration, at the end of the forty-eight hour withdrawal period and following the readministration of the drug, are tabulated in table 2, and the results of the staircase climbing tests in table 3. Chart 1 shows graphically a comparison of the results of the staircase climbing tests obtained during the three different phases of study.

The most significant positive observations in these studies were a definite increase in the number of white cells with a relative increase in the polymorphonuclear cells and a decrease in the lymphocytes at the end of the withdrawal period. Following the readministration of the drug, there was still a slightly further average increase in the number of white cells. Two cases, however, failed to show any increase in the number of white cells. On the other hand, one of our cases showed an increase in the number of white cells of from 8,100 to 27,000 at the end of the forty-eight hour period and reached 31,000 one hour after the readministration of the drug when all the withdrawal symptoms had apparently disappeared. A count taken six hours later showed a still further increase to 34,000. Twenty-four hours after the readministration of the drug, they had fallen to 14,000. This addict required 10 grains (0.65 Gm.) of morphine a day, the same amount required by one of our patients whose leukocytes numbered 8,300 at the beginning of the withdrawal period and who had the insignificant rise to

TABLE 2—*Studies of the Effect on Human Opium Addicts of the Abrupt Withdrawal of Morphine for a Period of Forty-Eight Hours and Its Readministration*

		Before Abrupt Withdrawal	At End of 48 Hour Abrupt Withdrawal	After Readminis- tration of Morphine at End of 48 Hour Withdrawal Period
Pulse rate while reclining	No cases	10	10	10
	Highest	80	71	83
	Lowest	52	50	54
	Average	64	61	69
Pulse rate while standing	No cases	10	9	9
	Highest	112	112	123
	Lowest	59	73	88
	Average	79	93	107
Blood pressure while reclining	No cases	10	10	10
	Highest	133/92	140/84	129/79
	Lowest	102/60	109/63	88/60
	Average	120/73	121/73	111/71
Blood pressure while standing	No cases	10	9	9
	Highest	130/90	138/94	112/90
	Lowest	86/64	110/74	80/60
	Average	110/79	116/85	98/77
Respiration	No cases	10	8	8
	Highest	22	24	34
	Lowest	12	11	12
	Average	17	16	17
Hemoglobin	No cases	10	10	7
	Highest	16.7	18.9	18.1
	Lowest	13.2	14.8	13.8
	Average	15.1	16.9	15.6
Erythrocytes	No cases	3	2	2
	Highest	4,827	5,150	5,550
	Lowest	4,450	4,300	4,500
	Average	4,609	4,700	5,025
Leukocytes	No cases	9	9	8
	Highest	13,100	27,800	34,000
	Lowest	7,500	7,800	8,000
	Average	9,800	15,200	16,980
Polymorphonuclears	No cases	7	9	7
	Highest	78	97	86
	Lowest	47	52	56
	Average	62	72	68
Lymphocytes	No cases	7	9	7
	Highest	46	40	39
	Lowest	20	2	12
	Average	33	25	27
Large mononuclears	No cases	7	9	7
	Highest	7	6	4
	Lowest	0	0	0
	Average	3	1	2
Eosinophils	No cases	7	9	7
	Highest	2	2	3
	Lowest	0	0	0
	Average	1	1	2
Basophils	No cases	7	9	7
	Highest	1	1	1
	Lowest	0	0	0
	Average	1	1	1
Urea	No cases	3	4	5
	Highest	15	16	18
	Lowest	11	10	11
	Average	13	13	15
Sugar	No cases	3	4	5
	Highest	101	115	126
	Lowest	69	85	93
	Average	93	101	107
Cholesterol, whole blood	No cases	10	7	8
	Highest	215	235	250
	Lowest	163	175	150
	Average	189	208	189

TABLE 2—*Studies of the Effect on Human Opium Addicts of the Abrupt Withdrawal of Morphine for a Period of Forty-Eight Hours and Its Readministration—Continued*

		Before Abrupt Withdrawal	At End of 48 Hour Abrupt Withdrawal	After Readminis- tration of Morphine at End of 48 Hour Withdrawal Period
$p_{H}$ blood	No cases	3	4	4
	Highest	7.51	7.51	7.45
	Lowest	7.37	7.43	7.35
	Average	7.45	7.46	7.42
Dry matter, whole blood	No cases	10	10	7
	Highest	22.7	24.5	23.3
	Lowest	20.1	21.7	16.2
	Average	20.7	22.6	21.9
Dry matter, cells	No cases	6	9	8
	Highest	40.8	43.6	35.3
	Lowest	33.2	37.5	27.4
	Average	41.3	40.7	41.2
Dry matter, plasma	No cases	10	10	8
	Highest	10.2	11.5	11.4
	Lowest	8.2	9.2	8.4
	Average	9.1	10.1	9.9
Schneider's score	No cases	8	7	7
	Highest	15	12	11
	Lowest	1	9	1
	Average	10.4	10	4
Oxygen percentage saturation of venous blood	No cases		6	6
	Highest		60.7	79.1
	Lowest		39.3	49.2
	Average		42.5	62.2
Red cells, per cent by volume	No cases	6	10	7
	Highest	38.7	43	45.0
	Lowest	34	37.3	35.0
	Average	36.2	40.2	39.1

8,500 at the end of the period. The two addicts who did not show a change in the number of leukocytes appeared to suffer as much as the other eight who showed definite increases.

The red blood cells were studied in only two cases and showed a slight rise after the abrupt withdrawal and a further slight increase following readministration of the drug in both cases. Determinations of hemoglobin by means of the Newcomer plate in ten cases showed an average rise of from 15.1 to 16.9 Gm., and in eight of these it remained practically the same after the readministration of the drug. The rise in hemoglobin occurred in all our cases as did the slight increase in the red cell volume following abrupt withdrawal.

The results obtained from the determination of the dry matter in the whole blood and plasma showed an average increased concentration of the blood of about 9 per cent. This tendency for a concentration was true in all the cases studied and following readministration of the drug did not return to the figure obtained before withdrawal. The dry matter of the cells remained unchanged.

Further studies showed no significant changes in the urea nitrogen, sugar and  $p_{H}$  of the blood. A slight rise of the cholesterol of the whole

blood was noted at the end of the abrupt withdrawal and a return to the same average figure following the readministration of the drug as that obtained before the withdrawal was begun. This rise of cholesterol was present in five of the seven cases studied.

In six cases studies of the percentage saturation of the venous blood drawn from the same vein at the elbow, following the abrupt withdrawal of the drug compared to the results obtained following the readministration of the drug, show an average increase in the percentage satura-

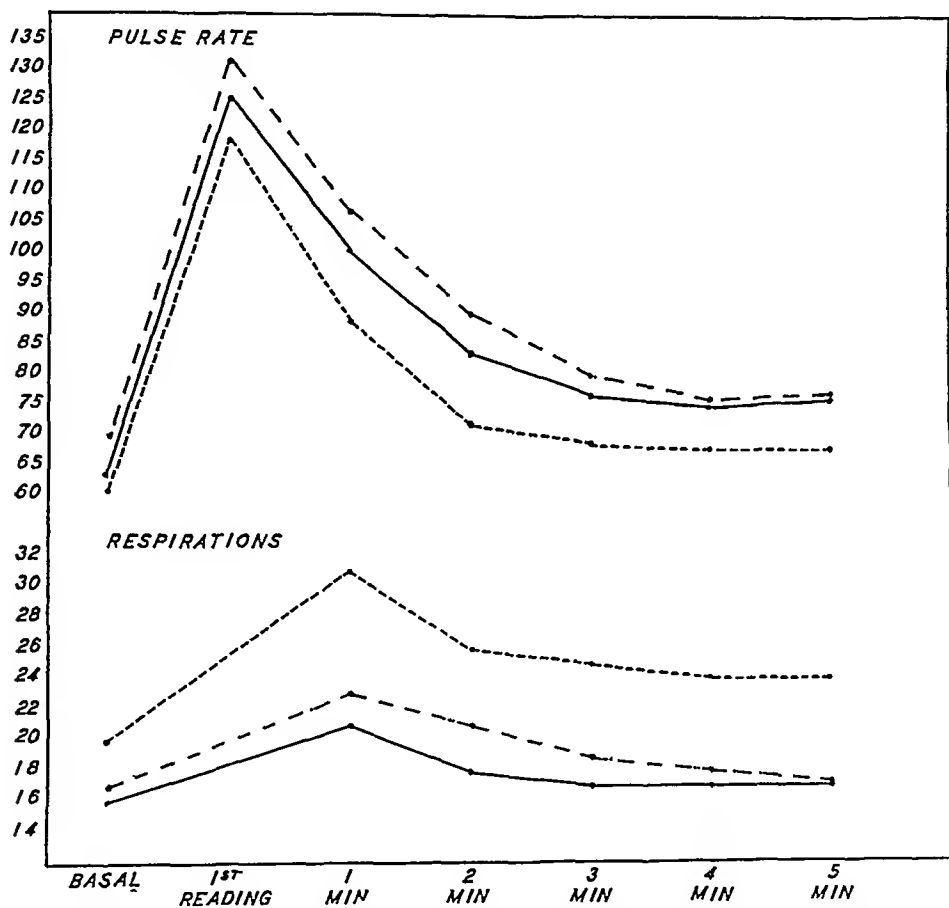


Chart 1—Average changes in pulse and respiration rates in response to the staircase climbing test in a group of human addicts receiving morphine, after withdrawal of morphine for forty-eight hours and following readministration of morphine after the forty-eight hour withdrawal period. In this chart and in chart 2 the solid line indicates, during administration, the broken line, after forty-eight hours, and the dash and dot line, following readministration.

tion of from 42.5 to 62.2 per cent. This rise in percentage saturation of the oxygen in the venous blood was present in all our cases.

The circulatory changes noted during these studies consisted in a slight fall of the average pulse rate while the patient was reclining during the abrupt withdrawal and a slight rise in the average rate following the readministration of the drug. A study of the individual

cases, however, shows this fall to be present in only six of the ten, the other four showing slight rises during the withdrawal period. The average rise of the pulse rate while the patient was reclining following the readministration of the drug occurred in nine of the ten cases, the other showing a slight fall in the rate.

The average pulse rate, determined while the patient was standing, increased fourteen beats per minute at the end of the forty-eight hour period, with a further average increase of fourteen beats following the readministration of the drug. In all individual cases, the patients showed this increase of pulse rate while standing following withdrawal

TABLE 3—*A Comparison of the Average Increase in the Pulse Rate, Respiration and Systolic Pressure and the Changes in Diastolic Pressure Following the Standcase Climbing Test on Human Opium Addicts Before Withdrawal, After a Forty-Eight Hour Period of Withdrawal of the Drug and Following the Readministration of Morphine*

	1st Reading	1st Minute	2d Minute	3d Minute	4th Minute	5th Minute
Pulse (9 cases)						
Before withdrawal	62	37	20	13	11	12
At end of withdrawal	58	27	11	8	7	7
Following readministration of drug	62	37	20	10	16	7
Respiration (9 cases)						
Before withdrawal		5	2	1	1	1
At end of withdrawal		11	6	5	4	4
Following readministration of drug		6	4	2	1	0
Systolic pressure (9 cases)						
Before withdrawal	29	30	25	16	9	4
At end of withdrawal	23	21	12	9	6	2
Following readministration of drug	18	19	15	13	8	4
Diastolic pressure (9 cases)						
Before withdrawal	-10	-7	-6	-6	-6	-6
At end of withdrawal	-6	-4	-2	-3	-0	-2
Following readministration of drug	-8	-1	2	4	3	7

compared to the figure obtained at the beginning of this period as well as the further increase following the readministration of the drug.

No change was present in the average systolic pressure, taken while the patient was reclining, at the beginning of the withdrawal period as compared to that at the end of the period. Individual cases, however, showed some marked changes. In one case, the systolic pressure rose 37 mm. In another it fell 20 mm. The others showed rises and falls ranging from 2 to 7 mm of mercury. An average rise of 6 mm in the systolic pressure was noted when the figures for the average systolic pressure determined while the subject was standing, following the withdrawal period as compared with those obtained at the beginning of this period. An analysis of the individual cases shows that four of the ten exhibited this rise, in two the pressure remained the same and in three it showed a slight fall. An average fall in the systolic pressure taken while the patient was standing was noted in the ten cases following

the readministration of the drug compared to the average systolic pressure, taken while the patient was reclining, at the beginning and end of this period. Seven of the ten cases showed this fall, in one the pressure remained the same and in the other two it showed slight rises. The greatest fall encountered was 23 mm.

Following the readministration of the drug, the systolic pressure taken while the subject was standing showed an average fall of 18 mm compared to the average obtained at the end of forty-eight hours and 12 mm compared to the average pressure at the beginning of the withdrawal period. Following the readministration of the drug, all cases without exception showed this fall in the systolic pressure while the patient was standing.

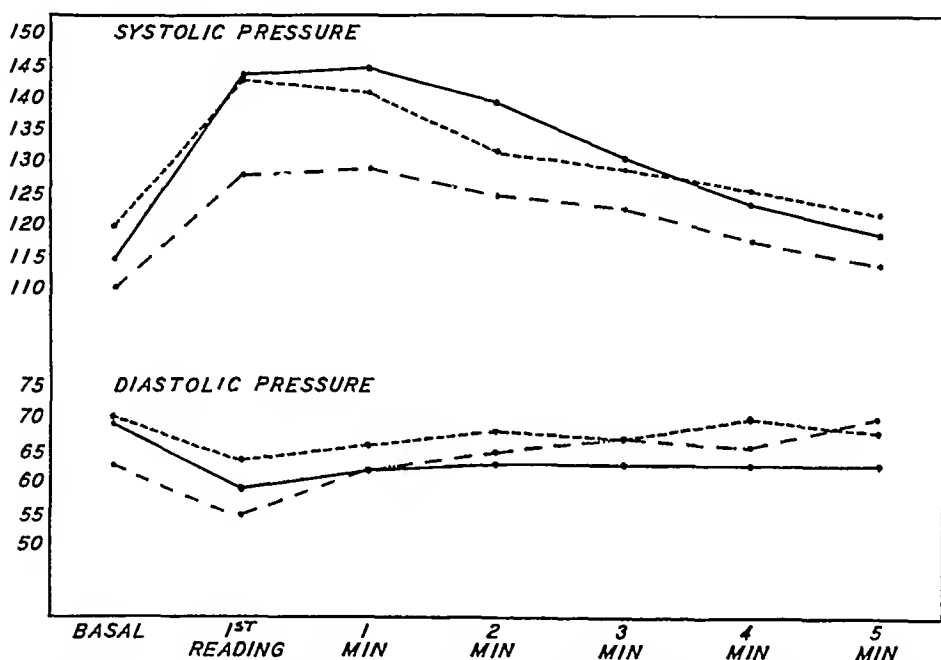


Chart 2—Average changes in systolic and diastolic blood pressure in response to the staircase climbing test in a group of human addicts receiving morphine, after withdrawal of morphine for forty-eight hours and following readministration of morphine after the forty-eight hour withdrawal period.

Schneider's test of physical fitness,<sup>2</sup> conducted in eight cases at the beginning of the withdrawal period, gave an average score of 10 points, the same as the average at the end of the forty-eight hour withdrawal period in seven cases. Following the readministration of the drug, the average score of the seven cases fell 6 points. This fall was directly due to the increase in the individual pulse rates and fall in the pressure when the subject changed from the reclining to the standing postures.

<sup>2</sup> Schneider, E. C. A Cardiovascular Rating as a Measure of Physical Fatigue and Efficiency, *J. A. M. A.* **74** 1507 (May 29) 1920.

Studies of the staircase climbing test at the beginning and end of the forty-eight hour period and following the readministration of the drug do not reveal any great changes in the response of the circulatory system to this rather fatiguing test. If anything, the response following the end of the forty-eight hour period when the addict complained of extreme muscular weakness was more similar to that of athletes than when the drug was being administered at regular intervals. The immediate increase in the respiratory rate at the close of the withdrawal period following the climbing of the staircase was the only indication of a poorer response to this test when compared to the test at the beginning of the period and following the readministration of the drug. The response following the readministration of the drug as measured by the reaction of a trained person was poorer than when the addict was suffering, except the respiratory increase. We found that trained normal persons met the stress of climbing with the greatest rise in pressure and the least rise in pulse rate, and showed the quickest return to normal.<sup>1</sup>

No changes were noted in the respiratory rates while the patient was reclining either at the end of the forty-eight hours or following the readministration of the drug as compared to the figures obtained at the beginning of withdrawal. Individual cases also showed only small and insignificant changes, with the exception of one case in which the respirations were 17 at the beginning of withdrawal, 20 at the end of the withdrawal period and 34 following the readministration of the drug.

Only two of our cases showed a slight rise in temperature during this period. The highest temperature reached was 100.2 F.

Chemical and microscopic examination of the urine showed the presence of a trace of albumin in two cases, but neither one showed the presence of any casts. All other examinations of the urine gave negative results.

Attempts to determine the basal metabolism of the gastro-intestinal tract, gastric analysis, ingestion of barium for roentgenograms and dextrose for dextrose tolerance tests were futile, the cooperation of the patient being so poor as to cause us to abandon the attempts.

The general behavior and symptomatology of these addicts were uniform during the forty-eight hour withdrawal period. All cases showed the characteristic pilomotor activity and the lacrimation, sneezing and excessive yawning. Five of the ten patients vomited, and all had normal bowel movements at the end of twenty-four hours. Three developed diarrhea at the close of the forty-eight hour period. In four cases, sweating was marked, beginning at the end of thirty-six hours. Muscular twitching, particularly of the muscles of the face and extremities, was present in all cases. One of our patients had a violent twitch-



ing of the muscles of the left leg which he himself attempted to stop by improvising a tourniquet by means of a towel. At the close of the forty-eight hour period, one addict complained of diplopia, and on examination he had a definite weakness of the right external rectus muscle. The average weight lost by the ten addicts was  $5\frac{3}{4}$  pounds (2.6 Kg), the individual losses ranging from 4 to  $8\frac{1}{2}$  pounds (1.8 to 3.8 Kg). The addicts presented a picture of dehydration, the features were drawn. The face, neck and upper anterior part of the chest had a peculiar color which we can describe best as a "dirty flush."

Not one of the addicts wished to continue the experiment following the twenty-four hour period, and the begging and pleading for morphine for the following twenty-four hour period became extremely trying. Our judgment in selecting these addicts to act as subjects was based on their willingness to cooperate when requested to do so while the drug was being administered. This judgment proved to be poor, for those who offered the least resistance in persuasion turned out to be the most annoying at the end of the first twenty-four hours of the withdrawal period. One patient refused absolutely to continue at the end of thirty-six hours unless given a  $\frac{1}{4}$  grain (16 mg) of morphine to help him through the remaining twelve hours. He was given a hypodermic injection of sterile water and promptly went to sleep for a period of eight hours, with a tourniquet which he had improvised from a towel on his left leg to prevent muscular twitchings. He was awakened by the pain resulting from too tight application of the tourniquet. This addict never became aware of the fact that he was given nothing but sterile water. We wish to state, however, that such dramatic results with hypodermic injections of sterile water are rare, in most instances the addict cannot be fooled with this substitution, particularly following treatment.

While the studies were being conducted, changes for the better in disposition and disappearance of abjection could easily be noted at the end of the forty-eight hour withdrawal period just prior to the readministration of the drug. The anticipation of the morphine that was soon to be had seemed to have a distinctly beneficial action. A few minutes after the administration of the drug, all the addicts complained of a heavy feeling in the stomach, usually they also smiled and said that they were now experiencing the heavy sensation in the stomach that would bring relief. Despite the fact that within half an hour the addicts said that they felt normal and stronger than ever, the muscular twitchings about the face were still present in some cases. The patient who developed diplopia during the withdrawal period claimed to be entirely normal within forty minutes except that he was seeing double. Tests of the ocular movements revealed the presence of a weakness of the right external rectus muscle for several hours following the readministration of the drug.

We found the cessation of lacrimation, sneezing, yawning, pilomotor activity, muscular twitchings, the return of normal color to the face and the changes in disposition most striking following the readministration of the morphine

#### COMMENT AND LITERATURE

Our observations covering the abrupt withdrawal periods resulted in a failure to find any symptoms or signs that have as yet not been described in the literature.<sup>3</sup> Our studies of the circulation, respiration and blood contribute nothing new, except for the discovery of a tendency toward a concentration of the blood and a slight rise in cholesterol during the abrupt withdrawal period. Morat<sup>4</sup> thoroughly described the appearance of leukocytosis at some time during the period of rapid withdrawal in a series of twenty-eight cases. Morat found this leukocytosis present in all his cases, whereas only eight of our ten cases showed it during the period of abrupt withdrawal. Studies of the blood of addicted dogs during withdrawal of the drug led Valenti<sup>5</sup> to the conclusion that vasoconstrictor substances were present in such blood, but this observation could not be confirmed by Pellini and Greenfield.<sup>6</sup> These authors were unable to detect any chemical changes in the blood of addicted dogs during the withdrawal stage. Plant and Pierce<sup>7</sup> found no change in the blood calcium of a dog who displayed violent symptoms during withdrawal of the drug.

We believe that our most important contribution to the study of withdrawal symptoms is the many negative observations obtained in these studies. This failure to find any marked changes, with the exceptions already mentioned, at the end of the withdrawal period as well as following the readministration of the drug, is open to criticism as we did not carry the experiments far enough. Our experience with these

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3 Communication from G. H. Smith, Esq., to Dr. Johnson. On Opium Smoking Among the Chinese, *Lancet* **1** 707, 1841-1842. Levinstein, E. Die Morphiumsucht, trans. by Charles Harrer, 1878. Sollier, P. La demorphinisation et le traitement rationnel de la morphinomanie, *Semaine méd.*, 1894, p. 146. Bishop, E. S. Narcotic Addiction, a Systemic Disease Condition, *J. A. M. A.* **60** 431 (Feb. 8) 1913.

4 Morat, D. Le sang et les sécrétions au cours de la morphinomanie et de la désintoxication, Thèse de Paris, 1911.

5 Valenti, A. Experimentelle Untersuchungen über den chronischen Morphinismus, Kreislaufstörungen hervorgerufen durch das Serum morphinistischer Tiere in der Abstinenzperiode, *Arch. f. exper. Path. u. Pharmacol.* **75** 437, 1914.

6 Pellini, E. J., and Greenfield, A. D. Narcotic Drug Addiction. II. The Presence of Toxic Substance in the Blood Serum in Morphine Habituation, *Arch. Int. Med.* **33** 547 (May 15) 1924.

7 Plant, O. H., and Pierce, I. H. Studies in Chronic Morphine Poisoning in Dogs. I. General Symptoms and Behavior During Addiction and Withdrawal, *J. Pharmacol. & Exper. Therap.* **33** 329 (July) 1928.

men at the end of a forty-eight hour period convinces us that such studies could be carried out only in institutions in which other methods than simple persuasion might be used

The incessant begging and the annoying behavior of the addict during the withdrawal period becomes at times almost unbearable and may well react on the casual observer, so warping his judgment as to lead to conclusions that would not have been reached except for the behavior of the addict. Any one dealing with this group of people is fully aware of the pernicious influence they exert. It has been our frequent experience to leave the wards with the firm conviction that these men are not organically sick, the whole picture being an emotional one, and that the viciousness attached to the picture could best be coped with in penal institutions. Just as frequently we have entered the ward and found these men suffering with violent muscular twitches, vomiting, perspiration and yawning and showing such a sickly appearance that we have been convinced that there must be an organic basis for their apparent suffering.

In favor of an emotional basis as a cause for the withdrawal symptoms, we wish to cite our negative observations. Despite the fact that the addicts claim to be so weak as to be scarcely able to move, their response to the staircase climbing test was carried out with the same efficiency as when drugs were administered, with the exception of the respiratory response, following the readministration of the drug, the response was, if anything, poorer. Such differences as exist in basal blood pressure, heart rate and respiratory rate are too small to indicate any significant change. Addicts will admit that when they are unable to obtain drugs and when withdrawal symptoms with extreme weakness have become severe, the assurance of an available supply at a considerable distance will cause them to travel this distance with remarkable speed and efficiency.

The concentration of the blood and loss of weight would indicate some organic disturbance, on the surface, but we believe that these two positive manifestations can be explained on the basis that the addicts will not take food or water and perspire to such an extent that they cannot help showing this loss of weight and the degree of concentration of blood found in our cases.

Yawning, restlessness, vomiting, diarrhea, perspiration and extreme weakness are found in many emotional states. This type of behavior has frequently been observed by one of us in a group of football players as well as in the coaching staff of a university football team just prior to the playing of a so-called "important game." Loss of appetite, marked restlessness, frequent yawning, diarrhea and, occasionally, vomiting constitute the picture. The players will state that they are so

weak that they can scarcely move, yet, when the whistle starting the game is blown, all fatigue quickly disappears

Further evidence that the picture of withdrawal symptoms has as its basis an emotional state is the response on the part of one of our addicts at the end of a thirty-six hour withdrawal period to the hypodermic injection of sterile water. Despite his obvious suffering, he immediately went to sleep and slept for eight hours. Addicts frequently speak about the "needle habit," in which the single prick of the needle brings about relief. It is not uncommon for one addict to give another a hypodermic injection of sterile water and the recipient to derive a "kick" and become quiet. On the other hand, it has been our experience just as frequently to have the addict know that he was given a hypodermic injection of sterile water and to have him fail to respond to its effect. Paradoxical as it may seem, we believe that the greater the craving of the addict and the severity of the withdrawal symptoms the better are the chances of substituting a hypodermic injection of sterile water to obtain temporary relief.

The presence of diplopia, marked increase in the number of leukocytes and albuminuria constitute sufficient evidence for one to look on withdrawal symptoms as having a true organic basis. Leukocytosis has been described in emotional states, but the degree reached in some of our cases, in four the leukocyte count being over 20,000 and in one reaching 27,000, would make one proceed with caution in the diagnosis of a clinical case before attributing such a count to pure emotionalism. Recently, however, Garrey<sup>8</sup> and his co-workers were able to establish a mental condition which frequently brings about an increase of from 100 to 300 per cent in the number of leukocytes. It is the belief of these observers that they are dealing merely with a redistribution due to fluctuation in the capillary bed in which leukocytes are trapped in the nonfunctioning capillaries.

White cell counts on the football players already cited made daily for a week before an important game and just prior to the game when they were showing symptoms of yawning, diarrhea and restlessness and complaining of extreme weakness failed to show any change from the normal count.

Muscular twitches are, at times, of such magnitude as to preclude any possibility of pure nervousness. The presence of albumin in the urine, mentioned by other investigators but curiously absent in this series of cases studied, is further evidence of the organic nature of these disturbances.

Failure of disappearance of the leukocytosis, diplopia and muscular tremors following the readministration of morphine when relief was obtained by the addict are difficult to explain. To those who are

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8 Garrey, W. E. Personal communication to the authors.

inclined to accept an emotional basis as the cause of withdrawal symptoms, a satisfactory explanation would be that the craving for the drug brings about emotional states sufficiently powerful to cause organic changes and that readministration of the drug brings mental relief long before the resulting organic changes can rectify themselves. On the other hand, if some true organic disturbance is the basis of the suffering, the readministration of morphine brings about relief from the peripheral sensations just as morphine relieves the patient from the pain of cancer but not from the cancer itself.

#### CONCLUSIONS

Abrupt withdrawal of morphine for a period of twenty-four hours in four addicts resulted in the appearance of mild withdrawal symptoms. These symptoms were accompanied by negligible changes in the pulse rate, leukocyte count and basal metabolic rate. Changes in behavior and irritability would indicate that mental suffering begins before physical suffering.

In ten addicts, abrupt withdrawal of morphine for a period of forty-eight hours resulted in the appearance of severe withdrawal symptoms. One case showed diplopia. These changes were accompanied by a definite leukocytosis in eight of the ten cases, concentration of the blood in all cases and a slight rise in cholesterol of the blood in seven of the ten cases. Albuminuria was found in two cases. The  $p_H$  of the blood, urea nitrogen and sugar showed no changes. Considerable loss of weight occurred during the forty-eight hour withdrawal period.

Following the readministration of the drug and relief from subjective symptoms, the increased leukocyte count and concentration of the blood remained for several hours, as did the diplopia and muscular twitchings of the face. A rise in the percentage saturation of the oxygen of venous blood was noted in all cases following the readministration of the morphine. The circulatory changes noted were a slight increase in the pulse rate and a slight fall in systolic pressure. The staircase climbing test and Schneider's test showed a decrease in the efficiency of the circulation following the readministration of the drug when compared to the results obtained at the end of the forty-eight hour withdrawal period.

# THE REGULATION OF BLOOD SUGAR IN IDIOPATHIC STEATORRHEA (SPRUE AND GEE-HERTER'S DISEASE)

## I THE LOW BLOOD SUGAR CURVE<sup>†</sup>

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The numerous investigations of the rise of blood sugar in the alimentary tract that have been carried out since the introduction of the micromethod for the determination of blood sugar have aimed chiefly to settle the borderline between the normal and the increased rise of blood sugar. The lack of rise or the small rise in blood sugar, the low blood sugar curve, on the other hand, has not attracted any particular attention. In the past year we have had occasion to investigate some instances of the low blood sugar curve. We believe it appropriate to call attention to these curves as constituting a somewhat overlooked phenomenon in the study of the regulation of blood sugar. We have found the low blood sugar curve most frequently present in one definite group of lesions, the idiopathic steatorrheas.

Our examinations of the blood sugar curve after ingestion of dextrose were made as follows:

The blood sugar was determined after the method of Hagedorn and Norman-Jensen. The amount of dextrose ingested was usually 60 Gm. In our first experiments, the blood was withdrawn at intervals of fifteen minutes, in the later experiments, the blood was taken every ten minutes, as we realized that frequent estimations of the blood sugar are important in determining the rise of the curve.

Although there are numerous reports on the rise of the blood sugar curve in normal persons after the ingestion of dextrose, it still has been difficult to find a fairly large number of observations that we could use in arriving at a definition of the term "low blood sugar curve." For such observations, to afford a control of value in our work, had to meet the following requirements: (1) the method employed in the blood sugar determinations had to be the same as that used in our experiments, (2) the amount of dextrose ingested could not differ to any extent from that given our patients, and (3) the intervals between

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<sup>†</sup> Submitted for publication, Nov 10, 1928

<sup>‡</sup> From the Medical Department, St Elizabeth Hospital, Copenhagen, Physician-in-Chief T E Hess Thaysen

the withdrawals of blood in any series had to be the same as those in our experiments. The first condition and the last were, of course, the most important.

Investigations of the rise of the blood sugar curve in normal persons after the ingestion of dextrose by the method of Hagedorn and Noiman-Jensen have been reported by Hagedorn,<sup>1</sup> Høst,<sup>2</sup> Lottrup-Andersen and Hansen.<sup>3</sup> As is well known, the rise of the blood sugar curve varies considerably in normal persons, and this variation follows the ordinary curve of error in the various observations. We therefore calculated the mean value of the rise of the curve and the mean error, by which we were able to estimate how often a curve of a definite height would be encountered in normal persons.

TABLE 1—*Calculation of the Low Blood Sugar Curve and Its Frequency in Normal Persons After the Ingestion of Dextrose from the Observations of Hagedorn, Høst, Lottrup-Andersen and Hansen*

Author	Number of Persons	Number of Tests	Mean Value of Rise, Mg per 100 Cc	Mean Error	Amount of Dextrose Ingested, Gm	Interval Between Tests, Minutes	Rise of 60 Mg per 100 Cc or Less Calculated Present, per Cent of Tests	Rise of 40 Mg per 100 Cc or Less Calculated Present, per Cent of Tests
Hagedorn*	20	39	75	20	47-100	15	25	5
Høst	21	27	74	20	50	15	25	5
Lottrup Andersen†	18	18	62	12	35	10	45	5
Hansen	5	19	61	16	30-100	2.5	50	10

\* Hagedorn's material consisted of two groups: a larger group of fourteen normal persons and a smaller group of six persons with metabolic disorders in their family histories. Here these groups are added together, since no other author made this distinction among normal persons.

† Lottrup Andersen's normal (?) persons were elderly people, most of them more than 60 years old.

In Lottrup-Andersen's investigations, the amount of dextrose ingested was small, and the same statement holds for some of Hansen's experiments, in which the rise of the curves is calculated after a mean curve that does not include the small increases of the blood sugar values. In Hagedorn's, Høst's and Lottrup-Andersen's material, we find a calculated frequency of a rise of 40 mg per hundred cubic centimeters or less in 5 per cent of the curves. In Hansen's material, on the other hand, this rise is found in approximately 10 per cent of the curves, which probably is due to the fact that this author calculated the rise from mean curves, not from the values obtained.

1 Hagedorn, H. C. *Undersøgelser over blodsukkerregulationen hos mennesker*, Copenhagen, Gyldendal, 1921.

2 Høst, H. J. *Metab. Research* 4:315, 1923.

3 Hansen, K. M. *Investigations on the Blood Sugar in Man*, Copenhagen, Nielsen and Lydiche, 1923.

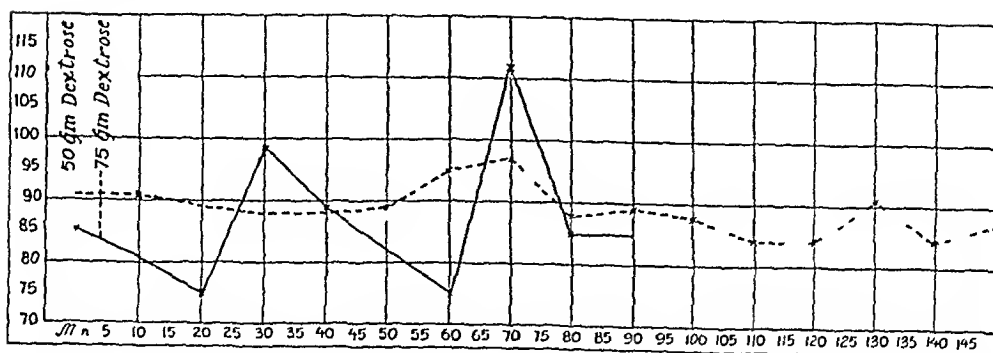


Chart 1—The blood sugar curves of a woman, aged 33, with nontropical sprue, after ingestion of dextrose (Holst's case) The broken line indicates total rise of 6 mg per hundred cubic centimeters (Nov 9, 1926), the unbroken line, total rise of 27 mg per hundred cubic centimeters (July 2, 1928)



Chart 2 (case 2, table 2)—Blood sugar curves of A B, a woman, aged 45, with nontropical sprue, after ingestion of dextrose The broken line indicates total rise of 20 mg per hundred cubic centimeters (Oct 26, 1927), the unbroken line, total rise of 28 mg per hundred cubic centimeters (Jan 6, 1928), the dotted line, total rise of 27 mg per hundred cubic centimeters (Feb 7, 1928)

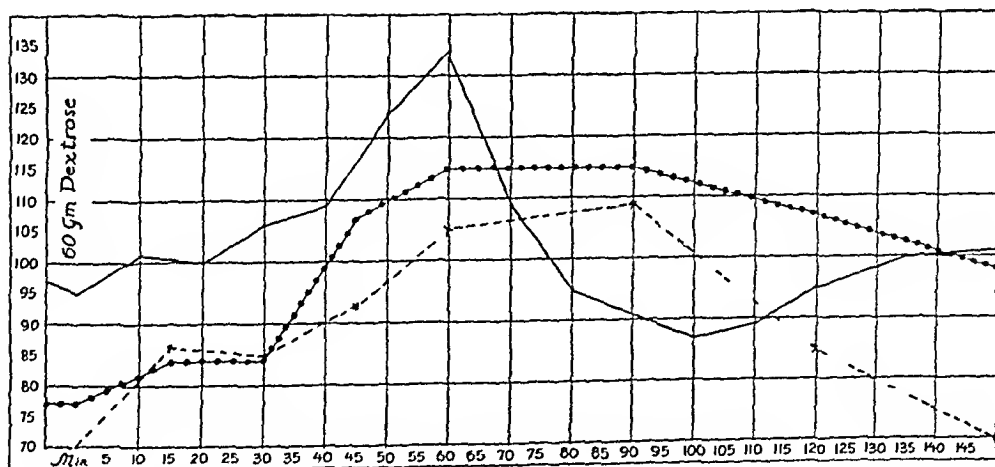


Chart 3 (case 4, table 2)—Blood sugar curves of E H, a woman, aged 38, with nontropical sprue, after ingestion of dextrose The broken line indicates total rise of 39 mg per hundred cubic centimeters (Nov 2, 1926), the dotted line, total rise of 38 mg per hundred cubic centimeters (Nov 3, 1926), the unbroken line, total rise of 37 mg per hundred cubic centimeters (Jan 21, 1928)



According to this calculation (table 1), the low curve then is encountered in 5 per cent of normal persons, granted that it is defined as a curve with a rise of 40 mg per hundred cubic centimeters or less, and provided that the blood is withdrawn at intervals of from ten to fifteen minutes, that the amount of dextrose ingested is approximately 60 Gm and that the blood sugar is determined after Hagedorn and Norman-Jensen's method

The low curve is characterized by the small height of its rise. One may also find a low-leveled curve that is characterized by a low starting point during fasting and a relatively low maximal value. We give some illustrations of such low curves demonstrated in cases of idiopathic steatorrhea

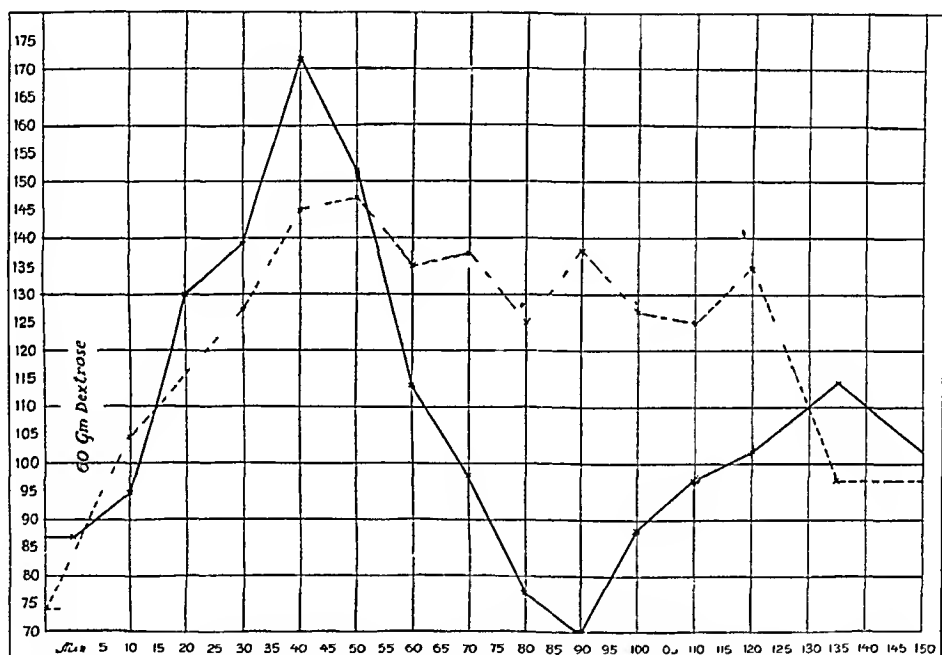


Chart 4 (case 8, table 2) —Blood sugar curves of S V, a woman, aged 56, with nontropical sprue, after ingestion of dextrose. The unbroken line indicates total rise of 84 mg per hundred cubic centimeters (Jan 27, 1928), the broken line, total rise of 73 mg per hundred cubic centimeters (Feb 28, 1928)

In the group of diseases designated "idiopathic steatorrhea," we include the following three: (1) tropical sprue, (2) nontropical sprue and (3) the lesion described by Gee<sup>4</sup> (1888) as "celiac affection" and by Herter<sup>5</sup> (1908) as "intestinal infantilism." The reasons for placing these three diseases together in one group and for this designation of the group will not be discussed in this paper. The low blood sugar

4 Gee, S. St Bartholmew's Hosp Rep 24 17, 1888

5 Herter, C. A. Intestinal Infantilismus, New York, The Macmillan Company, 1908, Wien, Franz Deuticke, 1909

curve here described is a symptom common to these diseases This has not been pointed out before

In a previous article on four cases of nontropical sprue, one of us (Thaysen<sup>6</sup>) emphasized that this lesion sometimes presents certain abnormalities of the blood sugar curve, i e., a very low rise of the curve after ingestion of dextrose This observation was later confirmed by Holst,<sup>7</sup> who pointed out that a slight rise of the blood sugar

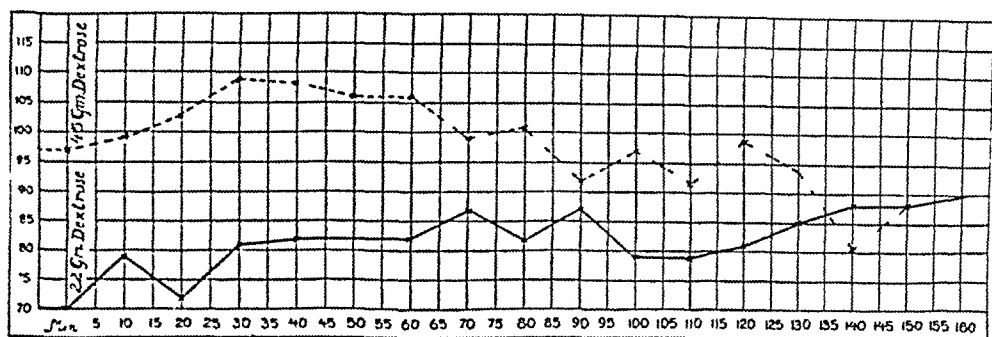


Chart 5 (case 9, table 2) —Blood sugar curves of E P, a girl, aged 11, with Gee-Herter's disease, after ingestion of dextrose The unbroken line indicates total rise of 15 mg per hundred cubic centimeters (Feb 25, 1928), the broken line, total rise of 12 mg per hundred cubic centimeters (Feb 26, 1928)

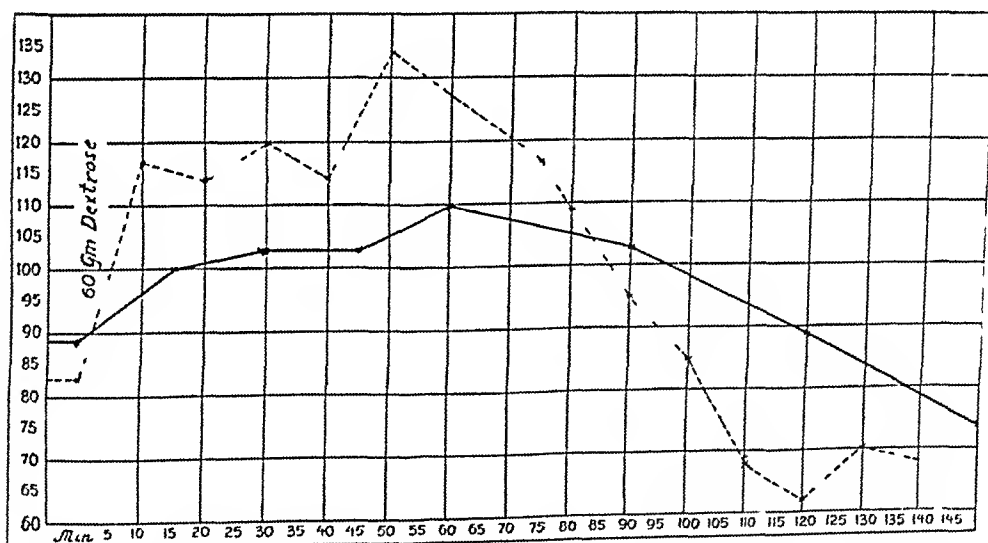


Chart 6 (case 10, table 2) —Blood sugar curves of V Ø, a man, aged 47, with tropical sprue, almost symptom-free, after ingestion of dextrose, slight alimentary glycosuria was noted, threshold approximately 130 The unbroken line indicates total rise of 21 mg per hundred cubic centimeters (Aug 12, 1927), the broken line, total rise of 51 mg per hundred cubic centimeters (March 1, 1928)

<sup>6</sup> Thaysen, T E H Acta med Scandinav 66 292 1926 Exact data on the blood sugar curve are available in only three of the four cases

<sup>7</sup> Holst, I A Acta med Scandinav 66 74, 1927

curve after ingestion of dextrose evidently is a phenomenon that occurs in nontropical sprue more frequently than was assumed in the paper mentioned

In the last two years, we have had an opportunity to examine two of the cases of nontropical sprue previously reported, and to investigate the blood sugar curves in four new cases of this lesion, in four cases of tropical sprue and in one case of Gee-Herter's disease (furnished by Prof C E Bloch) <sup>8</sup> Thus, our material consists of twelve cases of idiopathic steatorrhea in which the blood sugar was investigated To this is added the case reported by Holst

Table 2 gives a survey of all the cases of idiopathic steatorrhea, including determinations of the blood sugar, the weight and the height of the patients and the results of the analysis of the stools In regard to the technic in the determination of the metabolism, an article by Thaysen <sup>6</sup> may be consulted

Whereas one may expect to find a low blood sugar curve in about 5 per cent of normal persons, we found a low blood sugar curve in fifteen of thirty (50 per cent) patients examined who had symptoms of idiopathic steatorrhea (tables 2 and 4)

Of the sixty-four normal persons examined by Hagedorn, Høst, Lottrup-Andersen and Hansen, four presented a low curve on one examination Six of our eleven patients with idiopathic steatorrhea showed a low curve as an almost constant symptom, for two of our thirteen patients (nos 11 and 13) must be regarded as having recovered The low curve thus occurred much more frequently in this group than in the normal groups <sup>9</sup>

Two of the patients (table 2, nos 3 and 10) were examined twice, at intervals of one-half year and one month, respectively, each was

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8 Another patient with Gee-Herter's disease, recently admitted to the same department, showed likewise a low blood sugar curve after the ingestion of 32 Gm of dextrose, the total rise was 13 mg per hundred cubic centimeters of blood Dr E Svensgaard furnished us with the results of these examinations In a case of Gee-Herter's disease, Esp (Arbeider fra Rikshospitalets med Afdelinger, Oslo, 1927) found a rise of 39 mg per hundred cubic centimeters of blood

9 Although the difference between the frequency proportion of 5 per cent for normal persons and that of 50 per cent for the steatorrheic group is conspicuous, the small number of persons examined might yet give rise to some doubt as to whether the difference is real By calculating the mean error of the percentages given, this difference is found to be real

$$\sqrt{\frac{5 \times 95}{100}} + \sqrt{\frac{50 \times 50}{30}} = 11.2$$

To be real, the difference in the percentage of frequency between the groups with low curves (i.e., 50%—5%=45) must be at least twice as large as the figure (11) obtained after this formula, and so it is Consequently, the difference in frequency is an actual difference

TABLE 2—Survey of Cases of Idiopathic Steatorrhea

No	Diagnosis	Age	Sex*	Name	Weight, kg	Height, cm	Date of Determi- nation of Blood Sugar	Amount of Dextrose Admin- istered, Gm	Time Between Tests, Minutes	Value of Blood Sugar During Feasting, Mg per 100 Cc	Maximal Value, Mg per 100 Cc	Rise in Mg per 100 Cc	Famina- tion of Metabolism	Loss of Fat, Gm	Loss of Nitrogen, Gm
1	Nontropical sprue (Holst's case)†	33	♀		25.7	153	9/11/26 9/25/26	30 75	10 10	91 85	95 112	6 27	9/ 8/26	50.9	4.3
2	Nontropical sprue‡	43	♀	A. B.	50.0	161	11/26/27 1/ 6/28 2/ 7/28	60 60 60	15 10 10	104 90 87	121 118 114	20 23 27	11/ 1/27	22.2	2.0
3	Nontropical sprue§	44	♂	M.	50.5	180	9/10/25 1/20/26	50 30	15 15	62 71	89 115	27 41	9/ 8/25	25.9	2.1
4	Nontropical sprue#	38	♀	E. H.	61.7	163	11/ 2/26 11/ 3/26 1/21/28	60 60 60	15 15 10	70 77 97	109 115 131	39 38 37	11/19/27	20.8	3.0
5	Nontropical sprue	32	♂	E. N.	51.0	173	12/19/24 1/21/26 2/13/27 1/14/28	65 60 60 60	15 15 15 10	78 65 84 84	132 105 142 134	54 40 35 50	1/30/24 11/30/24	27.2 28.3	1.8 2.8
6	Nontropical sprue	54	♂	R. S.	57.1 50.3	150	7/20/25 3/ 2/28	50 60	10 10	73 85	128 138	53 53	3/ 7/28	66.7	2.7 1.0
7	Nontropical sprue	57	♀	K. W.	53.2	156	10/14/26 4/ 4/28	100 60	20 10	63 77	152 161	89 84			
8	Nontropical sprue	56	♀	S. V.	69.5	161	1/27/25 2/28/28	60 60	10 10	86 74	171 147	85 73	2/25/28 2/23/28	8.7 37.2	2.1 2.8
9	Gee Hertel's disease	11	♀	T. P.			2/25/28 2/26/28	22 44	10 10	70 97	87 109	17 12			
10	Tropical sprue	47	♂	V. O.	68.0	185	12/ 8/24 1/10/28	60 60	15 10	89 83	110 134	21 31			2.0
11	Tropical sprue	67	♂	W. S.	62.0	172	1/10/28	60	10	93	172	79			3.0
12	Tropical sprue	49	♂	C. A.	88.0	178	12/11/23	88	15	95	162	67	1/26/26	17.7	2.7
13	Tropical sprue	36	♂	H. K.	72.5	182	6/ 5/26	50	15	104	181	80			4.0

\* In this column, ♂ indicates male, ♀, female

† Microscopic examination showed no increase in fat content of feces

‡ Microscopic examination showed slight increase in fat content of feces Patient had glossitis

§ Microscopic examination showed feces normal Patient had no symptoms

# Microscopic examination showed slight increase in fat content of feces Patient had no symptoms

having a bad period at the time of the first examination and a relatively good period at the time of the second examination. Both showed a considerably higher rise of the blood sugar curve in the relatively good period than in the bad period. Two patients (nos 7 and 8) with a normal rise of the blood sugar curve were likewise having a good period with normal (no 8) or only slightly lowered absorption of fat, and without the pernicious anemia and the glossitis that were demonstrated during an attack of fatty diarrhea. Apart from certain nervous symptoms and an abnormality of the basal metabolism which caused us to count them in our total of nonrecovered patients, they were both symptom-free. These observations, together with the experiences before mentioned, indicate that the blood sugar curve becomes normal or rises higher when the patient improves.

In contrast with the normal blood sugar curve, which usually runs a regular course with a smooth fall down to or below the value during fasting, the low curves in idiopathic steatorrhea frequently are irregular in their course (charts 1 to 6), after-rises being not infrequent. These after-rises are encountered at an earlier stage of the curve than is the rule in the curve for normal persons, in which they occur chiefly at the end. In idiopathic steatorrhea, the after-rises are also higher than usual. In one instance (table 2, no 6, and chart 1), we saw an after-rise of 39 mg per hundred cubic centimeters, whereas the after-rise in Hagedorn's normal persons amounted to only 10 mg per hundred cubic centimeters or less. In other respects, however, it is impossible to give any collective description of the low blood sugar curve, as it varies not only among different persons but also in the same person on different examinations.

The length of the curve likewise varies a great deal, when the length is interpreted as the time it takes the curve to get back to the blood sugar value during fasting the first time. In seven cases, the low blood sugar curve got rapidly down to the value during fasting (within ninety minutes or less), but after this, in four of the seven cases an after-rise occurred, which went on to such a slow fall that the curve was not finished until from 151 to 180 minutes after its start. Two other low curves had not reached the blood sugar value obtained during fasting in two and one-half hours after the ingestion of dextrose, and one curve (chart 6) showed a steady rise in blood sugar for two hours—from 70 mg per hundred cubic centimeters to 90 mg per hundred cubic centimeters. On the whole, we had the impression that the low curves might be either shorter or somewhat longer than usual.

The blood sugar value during fasting is, on the average, somewhat lower than normal. In our patients, it was approximately 82 mg per hundred cubic centimeters. It was 88 mg per hundred cubic centimeters in Hagedorn's patients and 91 mg per hundred cubic centimeters in

Høst's patients From table 3, it is evident that the lower average value is due to the fact that blood sugar values of from 60 to 75 mg per hundred cubic centimeters were more frequent in our patients than in normal persons

Hypoglycemic values, i e, values below 70 mg per hundred cubic centimeters, were found in only three instances and as an inconstant phenomenon

In two of the cases (table 2, nos 5 and 6) the blood sugar curve was not low but low-leveled, the blood sugar value during fasting corresponding to the rather low values that were often found in the other curves, whereas the highest value obtained came to only 128 to 142 mg per hundred cubic centimeters, which is considerably lower than the usual maximal value in normal persons The entire curve was thus on a lower level than the curves found for normal persons

It is also worth noticing that the blood sugar value during fasting in those two patients (table 2, nos 7 and 8) who were examined dur-

TABLE 3—*Blood Sugar Values, Obtained During Fasting, Arranged in Groups*

Authors	60-75 Mg per 100 Cc., per Cent of Cases	75-95 Mg per 100 Cc., per Cent of Cases	95 Mg per 100 Cc., per Cent of Cases	Number of Cases
Hagedorn Høst and Hansen	5	75	20	113
Thaysen and Norgaard	25*	59	16	32

\* The usual calculation of the mean error in the percentages of the first group shows that there is a real difference in the frequency per hundred of the values in the group 60-75 mg per hundred cubic centimeters between Hagedorn's, Høst's and Hansen's patients and ours, as this difference is larger than two times the mean error, which is 9.2

ing a good period, and whose blood sugar curves showed a normal rise, was relatively low, just as in patients with low curves

The urine was examined repeatedly during the administration of dextrose It was found to be sugar-free for all patients but two (table 2, nos 5 and 10), the urine of these two occasionally gave a faint reduction of Fehling's solution In view of the fact that Høst found a faint glycosuria in six of twenty-five normal persons after the ingestion of dextrose (50 Gm dextrose in 200 cc of water), the slight elimination of sugar in the urine of these two patients hardly seems abnormal

Finally, we examined the urine of three patients (table 2, nos 2, 4 and 10) after their ingestion of 100 Gm of levulose, a test that is recommended by Strauss<sup>10</sup> as a functional test of the liver Neither Selivanoff's test nor Fehling's solution gave any positive reaction with urine voided one, two, three and four hours after the ingestion of levulose

The blood sugar curves found for one of the patients (table 2, no 4, and table 4) are worth mentioning in some detail, because they

show that a peculiar change in the curves set in at the same time that the patient showed pronounced signs of latent tetany. We have not found any analogous phenomenon mentioned in the literature.

Thus, the patient had a low blood sugar curve before the appearance of tetany and a normal rise of the blood sugar curve during a period with pronounced signs of tetany (marked facialis phenomenon, increased galvanic reaction, pains in hands and feet, but no convulsions). During this period, the blood sugar value during fasting, too, was considerably higher than before the onset of tetany. On treatment of the patient for tetany with rest in bed, calcium and a preparation of parathyroid, whereby the symptoms were reduced considerably, the blood sugar curve became low once more—lower than before—and the value during fasting went down to the same level as before. During a new period of marked symptoms of tetany, the curve again was higher, and

TABLE 4—*Blood Sugar in Patient in Whom Signs of Latent Tetany Developed*

Date	Value During Fasting	Rise, Mg per 100 Cc	Remarks
11/ 3/26	0 070	39	Fatty diarrhea, no tetany
11/ 4/26	0 077	38	Fatty diarrhea, no tetany
1/21/28	0 097	37	Fatty diarrhea, no tetany
3/13/28	0 091	77	Fatty diarrhea nearly gone, tetany
3/20/28	0 106	89	Fatty diarrhea nearly gone, tetany
4/ 4/28	0 086	21	Fatty diarrhea nearly gone, patient improved, treated with a preparation of parathyroid and calcium
4/17/28	0 105	60	Fatty diarrhea nearly gone, reappearance of tetany in spite of treatment with a preparation of parathyroid and calcium

so was the blood sugar value during fasting. Both curves went down low when the patient improved.

On Nov. 21, 1926, the calcium content of the blood was determined by A. Brems and found to be 10.86 mg per hundred cubic centimeters, which is a normal value. No more determinations of calcium could be made, as the veins in the arms of the patient were obliterated from numerous venipunctures, and the veins of the legs had been treated with injections for varices.

For that matter, tetany is a rather frequent phenomenon in idiopathic steatorrhea, it was demonstrated in no less than six of the thirteen patients (table 2, nos. 1, 3, 4, 6, 9 and 10). Of the seven patients without a sign of tetany, two (nos. 11 and 12) had recovered from the intestinal lesion, and two others (nos. 7 and 8) had improved considerably. Of the six patients with tetany, five (nos. 1, 3, 4, 9 and 10) had low blood sugar curves, the blood sugar curve of the sixth (no. 6) was really not low but, rather, low-leveled, with a low initial value and a relatively low maximal value. In the patient with Gee-Herter's disease (no. 9), the signs of tetany were present only on a

previous admission to the hospital, tetany could not be made out at the time that the blood sugar curves were examined

These observations, however, did not give an explanation of the peculiar connection between the manifestation of tetany and the higher rise of the blood sugar in patient E H (table 2 no 4, and table 4). One would rather expect the tetany to be a contributory cause of the low blood sugar curve. This view is supported by the experimental results of Underhill and Blatherwick<sup>11</sup> and Underhill and Nellan.<sup>12</sup> These authors found the blood sugar percentage in dogs falling to 0 after thyroparathyroidectomy. They thought that this hypoglycemia was caused by the absence of the parathyroid glands, since the symptoms of athyreosis subsequent to thyroidectomy do not develop for some time. They also stated that hypoglycemia, after the extirpation, was present before the appearance of tetany. These observations, however, are contested by Hastings and Murray,<sup>13</sup> who could not make out any decrease in blood sugar after the removal of the parathyroid glands. The investigations by Salvesen<sup>14</sup> are also at variance with these results, for he found the blood sugar curve normal in the acute stage of tetany, as well as in the latent stage after parathyroidectomy. Salvesen's curves, however, have the drawback that the determinations of the blood sugar were made at intervals of one-half hour. Salvesen thought that there was some connection between the calcium content of the blood and the tolerance of dextrose in parathyroidectomized animals, for the tolerance was lower when the calcium content of the blood was low. So neither the clinical experiences nor the experimental results give any adequate explanation of the connection between tetany and the rise of the blood sugar curve.

There is no demonstrable connection between the height of the blood sugar curve and the duration of the disease, but, apart from this, it is difficult to obtain any usable information about how long the patients have had steatorrhea. The blood sugar curve in patient 2 (table 2) was extremely low in spite of the fact that he had not definitely had steatorrhea more than one-half year, whereas the curves of patients 5 and 6 showed a higher rise, although they had suffered from steatorrhea for four years, at least.

We attach considerable importance to the rise of the blood sugar curve as a diagnostic aid in the classification of the diseases that come under the head of chronic steatorrhea. In the pancreatogenic form, we find a diabetic curve as the result of a lowered function of the pancreatic islands. There are exceptions, but in eight cases of pan-

11 Underhill, F. P., and Blatherwick, N. R. *J. Biol. Chem.* **18** 87, 1914

12 Underhill, F. P., and Nellans, C. F. *J. Biol. Chem.* **48** 557, 1921

13 Hastings, A. B., and Murray, H. A. *J. Biol. Chem.* **44** 233, 1921

14 Salvesen, H. *Acta med. Scandinav.* (supp 6), 1923, p. 1



creatogenic steatorrhea we saw only one in which there was a normal blood sugar curve. In alcoholic steatorrhea, the curve either is normal or shows a marked rise followed by a fall to hypoglycemic values. As shown by Meulengracht,<sup>15</sup> in this condition the blood sugar value may drop to 0.033 mg, or even down to 0.001 mg per hundred cubic centimeters.

How the matter stands in enterogenic steatorrhea from tuberculosis of the mesenteric lymph glands has not yet been studied so far as we know.

The frequent appearance of the low blood sugar curve in sprue is of further importance in connection with the question, still under discussion, whether sprue is related to or identical with pernicious anemia (Elders<sup>16</sup>). As the blood sugar curve in the latter, according to Johnsson<sup>17</sup> and Meulengracht and Iversen,<sup>18</sup> is most frequently normal or increased, one assumes that these observations are against such a relationship.

A later report will deal with some investigations of how the low blood sugar curves develop. For the present, it may be stated that for a number of patients with idiopathic steatorrhea the respiratory quotient before and after the ingestion of dextrose has shown that the dextrose is absorbed and metabolized. Thus, the low blood sugar curve cannot be due to any disturbance of absorption, which would otherwise be an explanation, as the chief symptom of these diseases, the fatty diarrhea, is due to impaired absorption of the fats in the food.

#### SUMMARY

The term "low blood sugar curve" has been proposed and defined as a curve with a rise of 40 mg per hundred cubic centimeters or less.

The frequent occurrence of low blood sugar curves in idiopathic steatorrhea (tropical sprue, nontropical sprue and intestinal infantilism) has been pointed out, and its differential diagnostic significance has been mentioned.

A case of nontropical sprue has been described, in which the low blood sugar curve became normal at the same time that the patient showed signs of tetany.

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15 Meulengracht, E. *Acta med Scandinav* (supp 26), 1928, p 181

16 Elders, C. *Indische Spruwes*, Gravenhage, 1918

17 Johnsson. *Acta med Scandinav* (supp 3), 1922, p 139

18 Meulengracht, E., and Iversen, Poul. *Deutsches Arch f klin Med* 148 1, 1925

# FURTHER OBSERVATIONS ON THE CONTOUR OF NORMAL AND OF TUBERCULOUS CHESTS \*

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The shape of the normal and that of the tuberculous chest are so strikingly different that a study of their diameters proves very interesting. A few years ago, while examining chests at the University dispensary, it appeared to me that the tuberculous chest was not flat, as is still a common belief, but rather round. This led me to carry on a series of measurements on normal and tuberculous chests, and I reported my observations in *The Journal of the American Medical Association* in 1927.<sup>1</sup>

Since that time I have made further observations on the contour of normal and of tuberculous chests and shall report them at this time. To make myself clearer, however, I shall give a brief review of my previous report.

The thoracic index, which is the ratio of the anteroposterior diameter to the transverse at the nipple line, was found to be greater in the tuberculous than in the normal chests. In 140 patients in whom a definite diagnosis of pulmonary tuberculosis was made, the average thoracic index was found to be 75.9 per cent, while in 166 students of the University of Minnesota, the average thoracic index was only 68 per cent.

The chests of ninety-nine normal school children and of fifty-one children at Glen Lake Sanatorium were measured. The average thoracic index for the normal children was found to be 71.6 per cent, and the thoracic index for the Glen Lake children was found to be 74.3 per cent.

In twenty-five cases of bronchial asthma and chronic bronchitis occurring in adults, the average thoracic index was 82.8 per cent, an interesting group of patients, forty in all, who came to the University dispensary with ailments of the chest, but who on physical and roentgen examinations disclosed no definite pathologic processes, showed an average thoracic index of 71.4 per cent.

These figures tend to show that the normal chest is approximately 11 per cent flatter than the tuberculous chest and 20 per cent flatter than the chests of persons with chronic bronchitis and asthma.

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<sup>1</sup> Submitted for publication, Jan. 30, 1929.

<sup>2</sup> Read before the Southern Medical Association, Rochester, Minn., Oct. 3, 1928.

\* From the Department of Medicine, University of Minnesota Medical School, and the Glen Lake Sanatorium, Oak Terrace, Minn.

1. Weisman, S. A. Contour of Normal and Tuberculous Chests, *J. A. M. A.* 89:281 (July 23) 1927.

The chests of children also show a definite difference

The vital capacity averaged 4,300 cc in the normal students and 2,650 cc in the tuberculous patients

In this paper, I shall report two further observations the length-width index and the length-depth index The length-width index is the ratio of the width of the chest to the length, and the length-depth index is the ratio of the depth of the chest to the length The length of the chest was measured from the lower border of the tenth rib to the upper margin of the outer third of the clavicle about 2 inches (5.08 cm) outside of the nipple line The width and the depth of the chest were taken at the nipple line An ordinary pelvimeter was used graduated with a centimeter scale

Just one hundred years ago Chomel<sup>2</sup> observed the difference between the shape of normal and of tuberculous chests Hutchinson,<sup>3</sup> in 1897, and again in 1903,<sup>4</sup> made a careful study of normal and tuberculous chests and showed not only that the tuberculous chest is rounder, but that it is narrower and deeper, and that it is a premature, undeveloped thorax, one approximating that of the quadruped type

The chest of the fetus is deeper than it is wide, as shown by the investigations of Muller<sup>5</sup> and Hutchinson A gradual development takes place until birth, as shown by Scammon and Rucker,<sup>6</sup> when the chest is almost round with a thoracic index of 86 per cent With the establishment of respiration it rises to 106 per cent, and it is about the third month before the thoracic index reaches the measurement it had at birth

The chest gradually changes in shape, becoming flatter, until about the twentieth year, as shown by a careful study by Zeltner<sup>7</sup> The vital capacity is greatest at this age, as shown by Stewart<sup>8</sup> From this time on the chest begins to change and assume a more rounded form until development ceases, in about the sixtieth year, as shown by Weisenberg<sup>9</sup>

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2 Chomel Mensuration du thorax, *Gaz d hôp* **1** 213, 1828-1829

3 Hutchinson, Woods Some Deformities of the Chest in the Light of Its Ancestry and Growth, *J A M A* **29** 512 (Sept 11) 1897

4 Hutchinson, Woods Is the Consumptive Chest Flat? *J A M A* **40** 1196 (May 2) 1903

5 Muller, Charlotte Zur Entwicklung des menschlichen Brustkorbes, *Morphol Jahrb* **35** 591, 1906

6 Scammon, R E, and Rucker, W H Changes in the Forms and Dimensions of the Chest at Birth and the Neonatal Period, *Am J Dis Child* **21** 552 (June) 1921

7 Zeltner, E Thorax Studien, *Munchen med Wchnschr* **66** 1407, 1919

8 Stewart, C A The Vital Capacity of the Lungs of Children in Health and Disease, *Am J Dis Child* **24** 451 (Dec) 1922

9 Weisenberg, quoted by Zeltner (footnote 7)

In 1904, Malone<sup>10</sup> showed by pantographic tracings that the healthy chest was wider and flatter than the tuberculous chest, and that in two chests of the same size, the one with a low thoracic index has a greater cross-sectional area and a greater vital capacity, as shown in figure 1.

From these facts one may assume that the chest of a person 21 years of age, having the diameter measurements of a child's chest is, in all probability, undeveloped. It is this type of chest which is more often associated with tuberculosis. I believe this to be true, as I will tend to show from a study of various diameters of the chest in a fair number of cases.

In order to check the results of my first report, I measured a new group of normal and tuberculous chests. This series consists of 443 students of the University of Minnesota and 316 patients from the Glen Lake Sanatorium, 132 females and 184 males. The children and the patients with asthma are the same as those measured before.

#### RESULTS

*Length-Width Index in Men*—For normal chests I measured 443 students of the University of Minnesota. The average length-width index was 78.4 per cent. This average, however, is over 9 per cent smaller than that shown in Hutchinson's series (85.5 per cent) of less than 100 cases.

The length-width index in my series of 184 tuberculous men was 77.1 per cent. This figure is also less than that (79.9 per cent) shown in Hutchinson's series of only nineteen tuberculous patients and that of Draper's<sup>11</sup> series (87.6 per cent) of seventy-five cases.

Hutchinson's results show that tuberculous chests are about 6 per cent narrower than normal chests, while in my series a difference of only about 1.7 per cent is shown. After I determined the probable errors in the normal and tuberculous series I found that the actual difference, in terms of probable error between the length-width index in normal and in tuberculous chests was only 2.5, which is perhaps not of great significance.

*Length-Width Index in Women*—The length-width index in 132 cases of tuberculous chests in women was slightly less than that in men, namely, 76.1 per cent. Draper's series of twenty-eight cases showed an average length-width index of 77.1, which is a difference of only about 1 per cent. From these figures, it appears that the tuberculous chest of a woman is narrower than that of a man.

10 Malone, F. R. The Relation of Chest Contour to Lung Capacity, J. A. M. A. **43** 783 (Sept. 17) 1904.

11 Draper, George. Human Constitution, Philadelphia, W. B. Saunders Company, 1924.

*Length-Depth Index in Men*—The length-depth index, which is the ratio of the depth of the chest to the length, showed a marked difference between normal and tuberculous chests. The length-depth index for the students averaged 52.5 per cent and for the tuberculous men, 59.7 per cent. The difference is 14.8 in terms of probable error, which is very significant. These figures tend to corroborate the observations of the thoracic index in my previous report, namely, that the healthy chest is the flat one, not the tuberculous chest.

Hutchinson's and Draper's series of cases, which have been mentioned before, show the length-depth index to be even deeper. Malone's series, too, showed that the length-depth index was greater in the tuberculous than in the normal person, as shown by a typical tracing (fig 1).

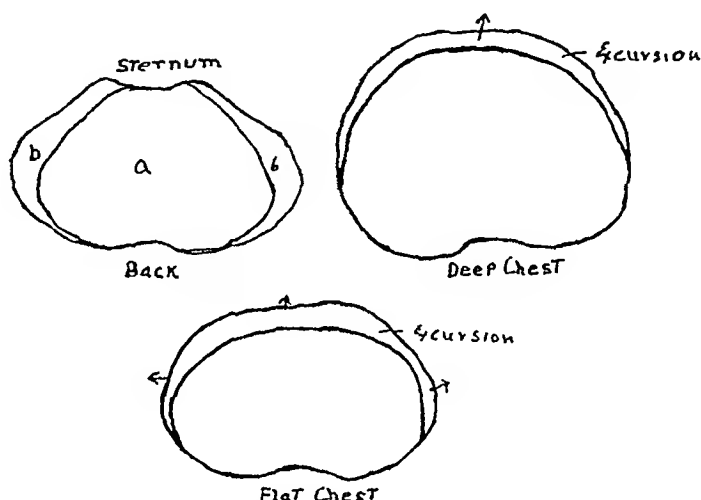


Fig 1—Pantographic tracings from Malone. In the tracing of the sternum *a* represents the deep chest and *b* the flat chest.

*Length-Depth Index in Women*—In an examination of 132 tuberculous chests in women, the length-depth index averaged 58.2 per cent, while in Draper's series of twenty-eight cases it was 64.7 per cent. Draper's series showed the chest of a woman to be deeper, while my series show the reverse. Draper's series, however, consisted of only twenty-eight cases. Rodes,<sup>12</sup> too, stated that in the negro the female thorax is rounder than the male thorax.

These measurements, therefore, show that the tuberculous chest of the adult tends to be narrower and definitely deeper than the healthy chest (fig 2).

*Measurements of Children's Chests*—The same group of ninety-nine Bremer school children was used for measurements of normal chests and fifty-one children from the Glen Lake Sanatorium for abnormal chests.

<sup>12</sup> Rodes, C. B. The Thoracic Index in the Negro, *Ztschr f Morphol u Anthropol* 9:102, 1906.

The average length-width index for the chests of fifty-four normal boys was 82.6 per cent, while that of the twenty-four abnormal chests was 84.8 per cent. Here the abnormal chest was the wider by 2.5 in terms of probable error. The same thing was found in the chests of girls. The length-width index for the normal child was 83 per cent and for the abnormal child 85.9 per cent, a difference of 2.9 in terms of probable error. This is probably more significant because of the fact that the average age of the abnormal children is less than that of the normal children by about two years.

There was, however, a noticeable difference in the length-depth indexes between the children in the normal and abnormal groups. The

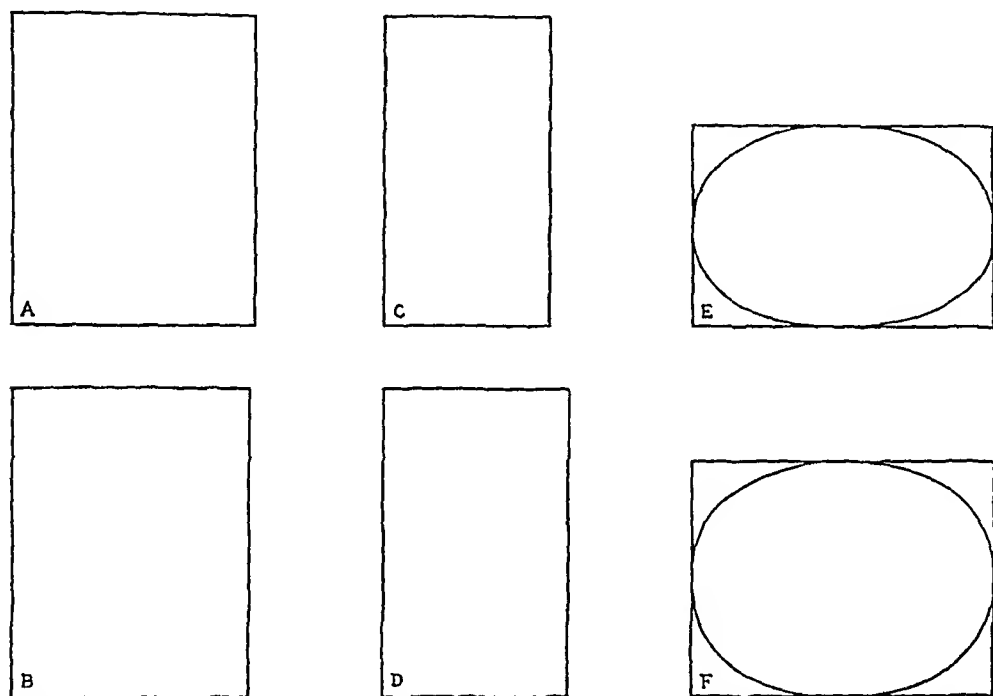


Fig 2—Diagrammatic sketch of chest diameters. *A* represents the length-width index of the normal chest, *B*, the length-width index of the tuberculous chest, *C*, the length-depth index of the normal chest, *D*, the length-depth index of the tuberculous chest, *E*, the thoracic index of the normal chest and *F*, the thoracic index of the tuberculous chest.

normal boys showed an average length-depth index of 59.3 per cent, while that of the abnormal boy was 62.6 per cent, a difference of 3.1 in terms of probable error.

The chests of the girls showed even a greater difference. The average length-depth of the normal girl was 58.6 per cent and that of the abnormal girl was 64.3 per cent, a difference of 6.9 in terms of probable error.

These children, although a diagnosis of active tuberculosis was not positively made in every case, showed a definitely deeper chest than the normal school children.

*Bronchial Asthma and Chronic Bronchiectasis*—There were eleven men and fourteen women with bronchial asthma and chronic bronchiectasis. The average length-width for the men was 82.2 per cent, a difference of about 6 per cent from the normal, but only about 1 in terms of probable error. The significant difference, however, is again in the length-depth index which is about 31 per cent or 4.5 in terms of probable error.

The average length-width index for the cases occurring in women is 76.4 per cent, and the length-depth is 59.9 per cent.

In Diaper's series of sixteen cases of asthma, consisting of five men and eleven women, the length-width index for the men was 86.4 per cent and for the women 90.7 per cent, the length-depth index for the men was 78 per cent and for the women 70.7 per cent.

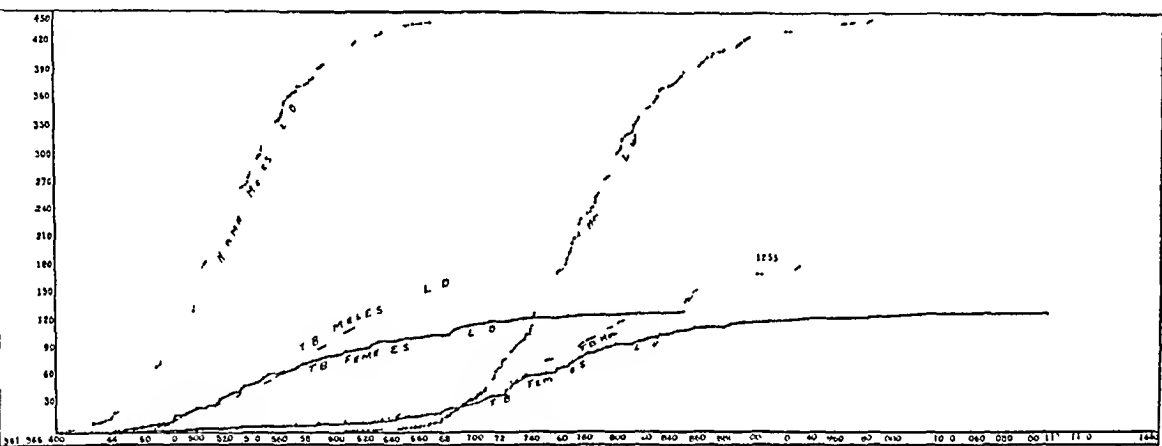


Fig 3—Comparison of the length-width and length-depth indexes of adults. The chests of 443 normal men and of 187 tuberculous men and 130 tuberculous women were measured.

From the figures thus far shown in this report and a close study of figure 3, one cannot help coming to the conclusion that the deep, narrow, round chest is more frequently associated with tuberculosis than the flat, wide one.

Respiratory diseases of the nose and throat are important factors in hindering the proper development of the chest (Hofbauer<sup>13</sup>). Chronic diseases, chronic bronchitis and asthma in early childhood also play an important rôle in affecting the proper development of the chest.

#### COMMENT

I should like to emphasize again the importance of measuring the chests of children as a routine so as to be able to select those children

<sup>13</sup> Hofbauer, Ludwig. Mund- und Nasenatmung in ihrem Einfluss auf die Thoraxbewegung, Arch f d ges Physiol 147 271, 1912.

# Summary of Indices of Thoracic Measurements

Type	Thoracic Index 67 27*	Length-Width Index	Length-Depth Index	Average Deviation			Probable Error			Difference in Terms of Probable Error		Age	
				Thoracic Index	Length-Width	Length-Depth	Thoracic Index	Length-Width	Length-Depth			Range	Average
Normal men	66 96	78 42	52 47	4 75	5 04	4 15	$\pm 0.202$	$\pm 0.214$	$\pm 0.177$			15 yr -47 yr	10 yr -2 mo
Tuberculous men	77 30	77 09	59 73	7 41	7 71	7 08	$\pm 0.431$	$\pm 0.486$	$\pm 0.462$	Thoracic index = 22 0 Length-width = 25 Length-depth = 14 8		18 yr 80 yr	36 yr 9 mo
Tuberculous women	72 10	76 05	53 20	5 76	8 21	7 39	$\pm 0.542$	$\pm 0.687$	$\pm 0.561$				
Normal children													
Male	72 4	82 55	59 28	4 46	3 90	4 02	$\pm 0.567$	$\pm 0.510$	$\pm 0.450$				
Female	71 0† 70 8	82 99	58 59	4 31	5 01	4 50	$\pm 0.525$	$\pm 0.610$	$\pm 0.529$			7 yr -15 yr	9 yr -11 mo
Tuberculous children													
Male	73 63	84 75	62 64	5 90	5 85	6 91	$\pm 1.03$	$\pm 0.978$	$\pm 0.974$	Thoracic index = 1 45 Length-width = 21 Length depth = 3 14			
Female	74 88	85 88	64 34	5 00	4 32	3 60	$\pm 0.830$	$\pm 0.765$	$\pm 0.644$	Thoracic index = 4 18 Length width = 29 Length depth = 69		4 yr 15 yr	8 yr
Chronic bronchitic asthma													
In men		82 2	68 8		8 17	8 12		$\pm 1.08$	$\pm 1.84$				
Both men and women	82 83			10 53			$\pm 1.63$						
In women		76 4	59 9		5 60	6 99		$\pm 1.53$	$\pm 1.71$				

\* 605 cases, including first series

† Deducting the tuberculous suspect



who show a chest that appears underdeveloped. This being done, proper exercises such as climbing ladders backward, climbing ropes and trees, work on parallel bars, gymnasium rings, baseball and tennis are desirable. Gotz <sup>14</sup> found that under the proper management and exercises the vital capacity of the lungs increased.

#### CONCLUSIONS

- 1 The tuberculous chest appears to be round, deep and narrow
- 2 The healthy chest tends to be flat and wide
- 3 There is evidence that exercise in early childhood can help to develop properly the undeveloped chest

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<sup>14</sup> Gotz, H. Modification of Child Chest by Gymnastics, *Monatschr f Kinderh* **30** 97 (May) 1925

# SUGAR TOLERANCE IN ARTHRITIS

## I CHRONIC INFECTIOUS ARTHRITIS<sup>1</sup>

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NEW YORK

Dietetic treatment for patients with chronic arthritis has exercised the minds of investigators and clinicians for many years. For a considerable time, it was believed that the proteins constituted an undesirable part of the diet of an arthritic patient. It was felt that an excess of uric acid in the blood was responsible for many conditions of the joints. This conception persisted until Garrod<sup>1</sup> demonstrated that in gout alone, of all the rheumatic conditions, there was a definite excess of any protein metabolite in the blood. In spite of this, there is still considerable confusion as to the rôle that the proteins play in the causation of disease of the joints. It may be stated at this time that, with the possible exception of those rare cases in which a definite food sensitization is present and is demonstrable by skin tests, the protein metabolism is normal in chronic arthritis.

In 1920, Pemberton and Foster<sup>2</sup> reported a diminished sugar tolerance in most cases of chronic infectious arthritis. They further demonstrated that the more severe the arthritis, the more diminished was the tolerance for dextrose. These observers also found that there was an increase in sugar tolerance after the removal of foci of infection, and concluded that the diminished sugar tolerance present in these cases was intimately associated with the presence of focal infection. Their observations were corroborated, in 1922, by the investigations of Fletcher<sup>3</sup> who found a diminished sugar tolerance in a large majority of his cases of chronic infectious arthritis described by him as the "periarticular arthritis of McCrae." He was unable to demonstrate, however, that the decrease in sugar tolerance in these cases was related to the severity of the disease.

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\* Submitted for publication, Dec 5, 1928

\* From the Cornell Clinic and the Medical Department of the Cornell University Medical College

1 Garrod, A. B. *Med Chir Tr London* **25** 83, 1848

2 Pemberton, R., and Foster, G. *Studies on Arthritis in the Army Based on Four Hundred Cases. III. Studies on the Nitrogen, Total Fat and Cholesterol of the Fasting Blood, Renal Function, Blood Sugar and Sugar Tolerance*, *Arch Int Med* **25** 243 (March) 1920

3 Fletcher, A. Almon. *Dietetic Treatment of Chronic Arthritis and Its Relationship to the Sugar Tolerance*, *Arch Int Med* **30** 106 (July) 1922

Since the initial work of Pemberton and Foster, the low carbohydrate diet has been in vogue with clinicians generally. This type of diet has been employed by me in the Cornell arthritis clinic for the past five years. After some time, it became apparent that the obese, middle-aged women who had the arthritis of the menopause were considerably helped by a restriction of their carbohydrate intake, but that the undernourished patients who had chronic infectious arthritis were unaffected by this form of treatment or, as happened more frequently, were made definitely worse by reduction of their caloric intake. The latter were often underweight to begin with, and a low carbohydrate diet produced in them a state of physical exhaustion without any compensating relief from their joint symptoms.

TABLE 1—*Clinical Data on Twenty Cases of Chronic Infectious Arthritis*

No	Name	Sex	Age	Weight, Pounds	Height, Inches	Average Weight Pounds	Blood Pressure	Duration	Severity
1	D R	F	32	135½	60	121	120/80	2 years	Moderate
2	A K	F	46	109	59¼	128	104/60	6 months	Mild
3	C R	M	53	165	64¾	148	154/94	2 years	Severe
4	E E	F	36	133½	61½	129	120/70	4 years	Severe
5	S E	F	37	104¾	62	127	121/80	5 years	Severe
6	V F	F	30	218	62½	127	114/60	18 months	Mild
7	J L	M	23	130	65¾	141	120/78	3 years	Mild
8	M B	F	47	139	64	141	120/70	Many years	Mild
9	B MeH	F	50	107	64½	144	104/70	8 years	Severe
10	H W	F	47	111¾	65	146	120/70	6 years	Moderate
11	D G	F	26	120½	60¾	119	110/70	18 years	Mild
12	D A	M	57	133	64½	145	110/65	5 years	Moderate
13	F K	F	26	106	61¼	119	110/60	5 years	Severe
14	I C	F	27	131	64½	130	110/60	2 months	Moderate
15	M T	F	31	150½	66½	139	120/82	1 year	Mild
16	G V	M	51	186	68¾	168	120/80	2 months	Severe
17	J M S	F	30	102	62	124	130/80	3 months	Mild
18	C N	F	48	104	62	136	130/90	10 years	Mild
19	L W	F	58	108½	57	127	150/80	10 years	Severe
20	M H	F	36	120½	57	117	122/80	10 years	Severe

These clinical observations led to an investigation of the sugar tolerance in the two types of arthritis described.<sup>4</sup> Forty cases were selected as a basis for this study—twenty cases of the arthritis of the menopause and an equal number of the chronic infectious type. These cases were all typical and presented the characteristic signs and symptoms of their group. This report is confined to a consideration of the infectious type.

As previously described,<sup>5</sup> chronic infectious arthritis is primarily a disease of early adult life, and manifests itself as a migratory, poly-articular condition of the joints, characterized by swelling, pain and stiffness of the parts affected. The fusiform finger joint presents the typical picture. As seen in table 1, there were sixteen women and four

4 Cecil, R. L., and Archer, B. H. Classification and Treatment of Chronic Arthritis, J. A. M. A. **87** 741 (Sept. 4) 1926.

5 Cecil, R. L., and Archer, B. H. Chronic Infectious Arthritis, Am. J. M. Sc. **173** 258 (Feb.) 1927.

men in this series. The average age was  $39\frac{1}{2}$  years, the average weight 130.8 pounds (59 Kg), and the average height 5 feet  $2\frac{1}{2}$  inches (1.59 meters). The normal weight for patients of this age and height is 133.8 pounds (60 Kg). The patients in this group were slightly underweight. The mean systolic blood pressure was 119 mm, and the mean diastolic pressure 74 mm. Two of the patients had a systolic pressure of 150 or more, but only one had a diastolic pressure of more than 90. One of the patients was found to have hyperthyroidism with a basal metabolic rate of plus 20. In one other case there was a suggestion of an endocrine dyscrasia. It has been shown that obesity,<sup>6</sup> hypertension<sup>7</sup> and endocrine dyscrasia<sup>8</sup> may influence the blood sugar curve. A study of the foregoing data shows that few of the extraneous factors that may influence the sugar tolerance were operative in this series.

#### METHOD

The dextrose tolerance test was conducted according to the method of Hamman and Hirschman.<sup>9</sup> The patient came to the clinic on the morning of the test without any breakfast. At 9 a. m., samples of blood and urine were obtained, and the patient was given 100 Gm of dextrose and 200 cc of water. At 9.30 a. m., samples of blood and urine were taken. At 10 a. m., this procedure was repeated, and the patient was given 200 cc of water. At 11 a. m., samples of blood and urine were obtained and the patient was again given 200 cc of water. At 12 m., the final samples of blood and urine were collected. All of the patients were given the dextrose by mouth as the intravenous route was felt to be impracticable and undesirable in this investigation. Lennox<sup>10</sup> showed that there was a general correspondence in the results obtained when using both the ingestion and intravenous methods of administering dextrose. Both Pemberton and Fletcher used the alimentary method in their research into this problem.

For the quantitative determination of the blood sugar the Benedict<sup>11</sup> modification of the Lewis-Benedict<sup>12</sup> method was used throughout. The tests were conducted in the Cornell Clinical Pathological Laboratory under the supervision of

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6 Paullin, J. E., and Sauls, H. C. Study of the Glucose Tolerance Test in the Obese, *South M. J.* **15** 249, 1922.

7 O'Hare, J. P. Glucose Tolerance Test in Chronic Vascular Hypertension, *Am. J. M. Sc.* **159** 369 (March) 1920. Herrick, W. W. Hypertension and Hyperglycemia, *J. A. M. A.* **81** 1942 (Dec. 8) 1923.

8 Janney, N., and Isaacson, J. The Blood Sugar and Thyroid and Other Endocrine Diseases. The Significance of Hypoglycemia and the Delayed Blood Sugar Curve, *Arch. Int. Med.* **22** 160 (Aug.) 1918.

9 Hamman, L., and Hirschman, F. L. Alimentary Hyperglycemia and Glycosuria as a Test for Sugar Tolerance, *Arch. Int. Med.* **20** 761 (Nov.) 1917.

10 Lennox, W. D. Blood Sugar, *Arch. Int. Med.* **40** 182 (Aug.) 1927.

11 Benedict, S. R. Note on the Determination of Blood Sugar by the Modified Picric Acid Method, *J. Biol. Chem.* **37** 503 1919.

12 Lewis, R., and Benedict, S. A Method for the Estimation of Sugar in Small Quantities of Blood, *J. Biol. Chem.* **20** 61, 1915.

Dr Thro In their original work Pemberton and Foster employed this method exclusively and found it satisfactory and well adapted for this type of investigation Fletcher used the Folin and Wu<sup>13</sup> technic for blood sugar determination

## COMMENT

The results of the tests are given in table 2

The mean level during fasting in this series was 0.108 per cent Half an hour after the ingestion of the dextrose, the mean reading for the group was 0.146 per cent At the end of an hour, this figure was lowered to 0.139 per cent, at the end of two hours, it was 0.119 per cent, after three hours, the curve dropped to 0.102 per cent The highest

TABLE 2—*Observations on the Blood and Urine*

No	Blood Sugar, Mg per 100 Cc					Urine Sugar				
	Fasting	½ Hour	1 Hour	2 Hours	3 Hours	First Test	Second Test	Third Test	Fourth Test	Fifth Test
1	107	125	115	100	75	0	0	0	0	0
2	100	150	125	100	75	0	0	0	0	0
3	107	125	150	136	115	0	0	0	0	0
4	100	150	150	125	100	0	0	0	0	0
5	107	150	125	100	100	Slightly reduced	Slightly reduced	+	0	0
6	100	150	136	100		0	0	0	0	0
7	125	166	150	125	120	0	0	0	0	0
8	100	150	125	115	100	0	0	0	0	0
9	100	150	125	100	90	0	0	0	0	0
10	107	150	136	107	100	0	0	0	0	0
11	115	150		187	150	0	0	0	0	0
12	120	166	150	150	125	0	0	0	0	0
13	107	125	115	75	60	0	0	0	0	0
14	107	125	150	125	107	0	0	0	0	0
15	115	150	136	125	115	0	0	0	0	0
16	125	166	187	136	120	0	0	0	0	0
17	88	125	136	100	75	0	0	0	0	0
18	125	166	136	100	100	0	++	++	0	0
19	115	136	166	150	115	0	0	0	0	0
20	100	150	136	125	107	0	0	0	0	0

level during fasting in the series was found to be 0.125 per cent and the lowest level 0.088 per cent The maximum concentration in any one case after ingestion of the dextrose was 0.187 per cent The minimum response was 0.125 per cent Glycosuria was present in only two cases of the entire series

To interpret properly the significance of the curves obtained it is necessary to set a normal standard The question of what constitutes a normal sugar tolerance curve involves two factors, namely, its height and its extent Various observers have given diverse figures as their conception of the maximum normal percentage of the sugar concentration in the blood after the ingestion of a test load of dextrose

13 Folin, O., and Wu, H. A System of Blood Analysis I. A Simplified and Improved Method for the Determination of Sugar, J Biol Chem **41** 367 (March) 1920

Jacobsen,<sup>14</sup> MacLean and de Wesselow,<sup>15</sup> Fletcher,<sup>3</sup> and Spence<sup>16</sup> considered 0.17 per cent as the upper postprandial limit in normal subjects. On the other hand, Hamman and Hirschman,<sup>9</sup> Pemberton,<sup>2</sup> and Hopkins,<sup>17</sup> believed that 0.15 per cent is the normal maximum concentration after giving dextrose. Still other observers have reported much higher figures. Goto and Kuno<sup>18</sup> found that the average fasting blood sugar concentration during fasting of 0.092 per cent rose to a maximum of from 0.125 to 0.185 per cent after the ingestion of dextrose, while Sakaguchi<sup>19</sup> gave from 0.133 to 0.191 per cent as the figures for the upper normal limit.

With so much discrepancy as to the maximum normal range following a test load of dextrose, it remained for Gray<sup>20</sup> to collect 452 sugar tolerance curves in clinically normal subjects and set a normal standard. This he did by analyzing 300 curves of this group which had been obtained after feeding 100 Gm. of dextrose or its equivalent. As the standards set by other observers are based on relatively small groups of cases, Gray's conclusions are important. The study of his 300 curves shows that the normal range is between 0.11 and 0.16 per cent, but that there is a large range of higher values. In his series of 452 curves obtained after giving various test loads of dextrose, sixty-five, or 14 per cent of the group, showed a maximum value of more than 0.17 per cent. In the group of 300 subjects given 100 Gm. of dextrose, thirty-eight, or 13 per cent, gave a maximum concentration of more than 0.17 per cent. This means that in one of seven curves there is apt to be a peak above 0.17 per cent, even in a series of clinically normal subjects. Gray, however, considered sugar tolerance peaks of more than 0.17 per cent as abnormal and, as he stated, "the definition of the import of values of

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14 Jacobsen, A. Untersuchungen über den Einfluss verschiedener Nahrungsmittel auf den Blutzucker bei normalen, zuckerkranken, und graviden Personen, *Biochem. Ztschr.* **56** 471, 1913.

15 MacLean, H., and de Wesselow, O. L. V. The Estimation of Sugar Tolerance, *Quart. J. Med.* **14** 103 (Jan.) 1921.

16 Spence, J. C. Some Observations on Sugar Tolerance, with Special Reference to Variations Found at Different Ages, *Quart. J. Med.* **14** 314 (July) 1921.

17 Hopkins, A. H. Studies in the Concentration of Blood Sugar in Health and Disease as Determined by Bang's Micro-Method, *Am. J. M. Sc.* **149** 254 (Feb.) 1915.

18 Goto, K., and Kuno, N. Studies on Renal Threshold for Glucose. *Arch. Int. Med.* **27** 224 (Feb.) 1921.

19 Sakaguchi, K. Beiträge zur Diabetesforschung. Erste Mitteilung. Ueber den Einfluss von Menge, Art und Zeit der Kohlenhydratzufuhr auf den Blutzuckergehalt beim gesunden Menschen, *Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo*, **20** 345, 1918.

20 Gray, H. Blood Sugar Standards, *Arch. Int. Med.* **31** 241 (Feb.) 1923.

0.17 per cent and over can justly be made only in the future when the after-history of these or similar exceptional subjects shall have been reported."

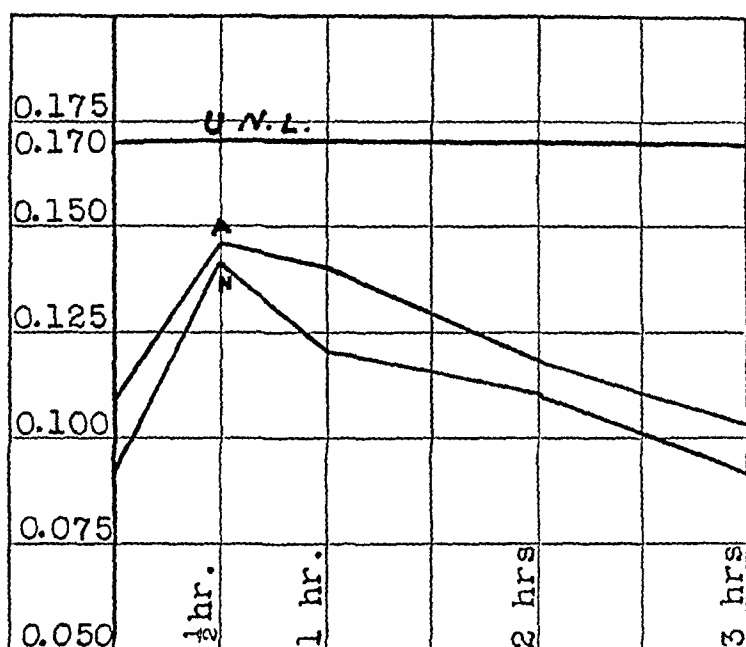
Fletcher took this figure as the upper normal limit, but Pemberton and Foster considered 0.15 per cent as the acme of blood sugar concentration after the feeding of 100 Gm of dextrose. As their conclusions were based on the examination of only eight normal subjects, it was felt advisable in this investigation to adopt the standard set by Gray.

Hamman and Hirschman,<sup>9</sup> in their original report, stated that after the ingestion of 100 Gm of dextrose, the resulting curve should return to normal in from two to three hours. This is conceded by practically all observers. MacLean and de Wesselow<sup>15</sup> found that the extent of the curve depended on the amount of dextrose given. When 25 Gm are fed to a normal subject, the curve drops to the predextrose level in ninety minutes, when 50 Gm are used, in about two hours, and, with greater amounts, in from two to three hours. Spence<sup>16</sup> also showed that the return to normal of the sugar tolerance curve depended on the age of the patient. There is a tendency in older subjects to have a higher and more prolonged curve.

If a postprandial reading of blood sugar of more than 0.17 per cent is considered to be an evidence of a diminished tolerance for dextrose, one finds that only two cases, or 10 per cent of the series, fall into this category. In case 11, the maximum concentration reached was 0.187 per cent. This was the figure for two hours, the figure for one hour is unavailable, because insufficient blood was obtained to perform the test. It is reasonable to suppose that the figure for one hour would have been even higher than 0.187 per cent. As the curve was still at 0.15 per cent after three hours, this case was definitely one of diminished sugar tolerance. It is interesting to note that this was a mild case of chronic infectious arthritis, although one of long duration. Case 16 likewise showed a high maximum concentration (0.187 per cent), but the return to the predextrose level was made in three hours. This was a case of severe infectious arthritis of short duration in a man, aged 51.

Three cases, or 15 per cent of the group, had a normal peak, but the curve failed to return to the predextrose level in three hours. In patient 3, aged 53, with a predextrose level of 0.107 per cent the reading was still 0.115 per cent after three hours. In case 12, the reading ranged from a fasting level of 0.12 per cent to 0.125 per cent after three hours. In patient 20, aged 36, with a concentration during fasting of 0.1 per cent, the reading was 0.107 per cent in three hours. The average difference in the two levels in the three cases was only 6 mg per hundred cubic centimeters. The average age was 49, which probably accounts for the slight variation from the normal. However patient 20, aged only 36, may be considered to have had a slightly diminished sugar tolerance.

Only one case (11) of the entire series showed both a maximum concentration of more than 0.17 per cent and a failure of the curve to return to the predextrose level in three hours. Including case 16 with a maximum concentration of more than 0.17 per cent and case 20 (a patient, aged 36) in which the curve failed to return to normal in three hours, there were three cases, or 15 per cent of the series, with abnormal curves. This corresponds rather closely with the observations of Gray<sup>20</sup> who reported departures from the normal in 13 per cent of his series. In the accompanying chart is seen the mean curve of the entire series as contrasted with the mean curve of Gray's 300 normal patients who were submitted to the same test.



Average curve for the series, contrasted with the normal curve of Gray. *N* represents the normal curve, *A*, the average curve, and *U.N.L.*, the upper normal limit (0.170 per cent) as established by Gray.

The predextrose level of the present series (0.108 per cent) is considerably higher than that of Gray's (0.09 per cent). This may be due to the higher average age of the group. Gray failed to give the average age in his series of cases, although Spence showed that the age factor is important in interpreting the results for sugar tolerance. In the present series, the average maximum concentration after the feeding of dextrose was 0.146 per cent as contrasted with the normal maximum of 0.14 per cent. The normal increase in blood sugar concentration, however, one-half hour after giving 100 Gm of dextrose, is 0.05 per cent. In this group the average increase one-half hour after the test load was only 0.038 per cent. As the level for the half hour is usually the maximum figure obtained, this tends to indicate that a greater tolerance was present.



in the series than in normal subjects. In one hour, the normal figure is 0.03 per cent above the predextrose level, and in the arthritic group it is 0.031 per cent. The normal curve returns to its original level in three hours. In this group there was a slight drop below the predextrose level, a phenomenon which has been found to be a common occurrence in normal subjects.<sup>21</sup>

Although the presence of postprandial glycosuria as a test for sugar tolerance has been discarded, it is interesting to note that only two patients, or 10 per cent of the series, showed glycosuria after the ingestion of 100 Gm of dextrose. This is in marked contrast with the normal figure established by Gray, who found that 40 per cent of 129 normal patients showed glycosuria after a similar test load of dextrose.

Pemberton and Foster expressed the belief that the sugar tolerance in chronic infectious arthritis varies directly with the severity of the disease. They found that the more severe the arthritis, the more diminished was the tolerance for dextrose. As shown in table 1, there were eight mild cases in the present series, four that were considered moderate and eight in which the process was thought to be severe. The mean maximum reading in the mild cases was 0.157 per cent, the average rise from the predextrose level was 0.049 per cent. In only one case was there failure to return to the original level in three hours. The average peak in the moderate cases was 0.148 per cent, the average rise from the predextrose level was 0.037 per cent. In one case, there was a slight increase over the predextrose level after three hours. In the eight severe cases the average maximum reading was 0.153 per cent, the post-dextrose rise was 0.046 per cent. In two of the cases, the curves failed to return to the predextrose level in three hours, but in one of these the patient was 53 years of age and there is little significance to the slight discrepancy present. As already mentioned, case 20 (a patient, aged 36) may be considered as showing a slightly diminished sugar tolerance. The highest average peak, and the highest average increase in blood sugar concentration after a test load of dextrose were both found to be present in the mild cases. The severe cases showed lower peaks and the moderate cases the lowest average blood sugar concentration of the three groups. In each of the three categories, there was one case in which the curve failed to return to normal in three hours. It is apparent from these observations that there is no relationship between the sugar tolerance and the severity of the arthritic process. This is in accord with the observations of Fletcher.<sup>3</sup>

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21 Folin, O., and Berglund, H. J. Some New Observations and Interpretations with Reference to Transportation, Retention and Excretion of Carbohydrates, *J Biol Chem* **51** 213 (March) 1922. Leifmann, E., and Stern, R. Ueber Glykaemia und Glykosurie, *Biochem Ztschr* **1** 299 (July 18) 1906.

Pemberton and Foster<sup>2</sup> also demonstrated a relationship between foci of infection and sugar tolerance. Their observations were corroborated by Pringle and Miller,<sup>22</sup> and more recently by Evans, Riding and Glynn.<sup>23</sup> The original observers found that the removal of definite foci of infection was followed soon after by an increase in the tolerance for dextrose. In the present series, foci of infection were demonstrable in eighteen of the twenty cases (table 3). In five cases more than one focus of infection was present. Diseased tonsils, alone or in combination with other foci, were the source of infection in fifteen, or 75 per cent, of the cases. Apical abscesses, alone or in combination with other foci, were present in five cases, or 25 per cent of the series. Pyorrhea, both mild and moderate, was found in a number of patients, but was not thought severe enough to be considered as a source of infection. The proportion of cases of tonsillar infection to those of infection of the

TABLE 3—*Foci of Infection and Their Relationship to the Sugar Tolerance Test*

No	Name	Foci Present at Time of Test	Foci Removed Before Test	No	Name	Foci Present at Time of Test	Foci Removed Before Test
1	D R	None	Tonsils	11	D G	Tonsils	None
2	A K	Tonsillar stubs, teeth	None	12	D A	Sinuses, epididymus	None
3	O R	None	Tonsils	13	R K	None	Tonsils
4	E E	Tonsils	None	14	E C	None	Tonsils
5	S E	None	Tonsils, teeth, cervix	15	M T	Tonsils	None
6	V F	Tonsils, cervix	None	16	G V	Prostate, tonsils	None
7	S L	Teeth	Tonsils	17	J M S	Sinuses	None
8	M B	None	None	18	C N	None	Teeth
9	B McH	Bronchi	None	19	L W	Tonsils	Teeth
10	H W	Tonsils	None	20	M H	Tonsils	None

teeth is a little higher in this group than in the larger series of cases of infectious arthritis reported a year before the present article. Other organs considered to harbor foci were the sinuses (two cases), the cervix (two cases), and the prostate, epididymus and bronchi (one case each).

All of these cases were active, and the patients were under treatment at the clinic. None could be considered as belonging to the group which Pemberton and Foster in their report called "convalescent." As shown in table 3, active foci were present at the time that the sugar tolerance test was performed in thirteen, or 65 per cent, of the cases. Original foci had been removed but the disease was still active at the time the test was given in six cases, or 30 per cent of the series. In two cases, original foci had been removed but other foci were present and active.

<sup>22</sup> Pringle and Miller. Glucose Tolerance in Chronic Arthritis, *Lancet* 1 171 (Jan 27) 1923.

<sup>23</sup> Evans, Riding, and Glynn. The Influence of Oral Sepsis upon Carbohydrate Tolerance in Non-Diabetics, *Lancet* 2 592 (Sept 17) 1927.

at the time of the sugar tolerance determination. In one case, there was no demonstrable focus nor did the history throw any light on any original source of infection.

The average maximum blood sugar concentration in the thirteen cases with demonstrable foci was 0.158 per cent. The average predextrose level of this group being 0.108 per cent, it is found that after a test load of dextrose, there was an increase in blood sugar concentration of the exact normal figure (0.05 per cent). The average maximum concentration of the blood sugar in the six cases with evidence of a definite arthritic process but with eradicated foci was 0.144 per cent. The average predextrose level for this group was 0.11 per cent. The average increase in concentration after the ingestion of dextrose was only 0.034 per cent as compared with 0.05 per cent in the former group. This might be interpreted to mean that in cases of infectious arthritis with active foci there is less tolerance for dextrose than in those in which the foci have been eliminated. Against this assumption, however, is the fact that those cases in which foci are active show no deviation from the normal standard as established by Gray. One must conclude therefore, that there is no definite evidence at hand to prove that focal infection has any specific effect on sugar tolerance.

#### CONCLUSIONS

1 In a study of twenty typical cases of chronic infectious arthritis, no evidence was found of a diminished sugar tolerance.

2 The sugar tolerance in this disease does not seem to vary with the severity of the process.

3 Foci of infection apparently have no specific action on the sugar storage mechanism.

# FRUCTOSURIA \*

P A HEERES, M D

AND

HERMAN VOS, M D

GRONINGEN, HOLLAND

## REPORT OF CASE

*History*—Early in August, 1927, a servant girl, aged 23, was admitted to the medical clinic of the University Hospital at Groningen, Holland, because her physician could not find an appropriate diet after having treated her for three years for a condition he thought was diabetes. Backache was the complaint which led the girl to see a physician, and he had found reducing properties in her urine. At that time, the patient had been drinking a good deal, the quantity of urine passed was abundant and the appetite was normal. A diet was prescribed, from which sugar and sweet foodstuffs were omitted, with potatoes and bread in moderate quantities. The backache disappeared, but the urine was not always sugar-free. The physician further informed us that the urine passed at night never contained any sugar, while that passed during the day at times showed reducing properties.

About a year prior to consulting the physician, the patient had suffered from pleurisy with effusion, and she had been resting several months. No cough or expectoration had been present, and some emaciation only at first.

The personal and family history did not contain any data of special significance, there was no familial tendency toward diabetes.

*Examination*—The patient was fairly well nourished, healthy looking and of normal build. She weighed 61.3 Kg. The skin and mucous membranes were normal, the lymph glands were not enlarged. The pulse rate and respirations were not abnormal. The blood pressure was 120 systolic and 75 diastolic (Riva-Rocci technic). The cranial nerves functioned well, the tongue was slightly coated. The teeth showed caries, pyorrhea alveolaris and defects, the tonsils were not swollen. The thyroid was slightly enlarged, and the trachea not displaced. The thorax was moderately arched, the right half was sunken, and there was less expansibility than on the left side. The heart was normal on percussion and auscultation. The lower border of the right lung was a little higher than the left and moved less freely. On the right anteriorly, the percussion note was shorter, with weakened respiration and a few crepitant râles. The abdomen, spine, genitals and extremities did not show any abnormalities. All reflexes were normal. The roentgenogram of the thorax revealed no abnormalities except slight traces of pleurisy and small infiltrations in the right upper lobe. The Pirquet reaction was positive, the Wassermann reaction negative.

The differential leukocyte count was as follows: eosinophils, 1 per cent; neutrophil juvenile forms, 0.5 per cent; band forms, 13 per cent; polymorphonuclears, 50 per cent; lymphocytes, 32 per cent; monocytes, 3.5 per cent.

The sedimentation rate was 22 mm. in the first hour (Westergreen).

The patient, therefore, showed signs of mild pulmonary tuberculosis, for which, after observation in this clinic, she was treated in a sanatorium with excellent results.

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\* Submitted for publication, July 24, 1928.

\* From the Clinic for Internal Medicine, Prof. Polak Daniels, Director.

The phenomena of a disturbed carbohydrate metabolism deserve special attention. On her admittance, the urine reduced both Fehling's and Nylander's solutions, besides showing a trace of acetone but no diacetic acid. The polarization plane was turned to the left, and our suspicion that the reducing substance was not dextrose but fructose was proved by the following tests:

- 1 After fermentation, the urine did not reduce the solutions
- 2 The urine showed the Seliwanoff reaction
- 3 The reaction of Bang<sup>1</sup> was also positive (heating on addition of ox gall and strong hydrochloric acid). It may therefore be safely asserted that the patient excreted levulose with the urine.

#### LITERATURE AND COMMENT

From the literature, three forms of fructosuria are known:

1 There is a special alimentary levulosuria occurring in conditions of the liver parenchyma, such as hepatic cirrhosis, catarrhal jaundice, hepatic syphilis, etc., to which Strauss<sup>2</sup> first called attention. This alimentary fructosuria has even become a much applied test of liver function. Later, for the estimation of the hepatic function, the galactose test came to be regarded as of great value, although the significance of the first is still highly appreciated by many investigators (for instance, King<sup>3</sup>).

2 It does not seem to be rare in diabetes mellitus, particularly in severe cases, for the patients to excrete not only dextrose, but also fructose, in the urine. Different estimations of the frequency of this condition have been given by various authors. Von Noorden regarded fructosuria in diabetes mellitus as a *signum mali ominis*.

3 True fructosuria, in the absence of any hepatic disturbance and of diabetes mellitus, is a rare condition, of which so far about fifteen cases<sup>4</sup> have been recorded, and only two of these were investigated with a fair degree of completeness<sup>5</sup>. In this form of fructosuria, levulose is excreted with the urine, if this sugar, as such, or as a constituent of

1 Bang. *Lehrbuch der Harnanalyse*, Wiesbaden, Bergmann, 1918, p. 119.

2 Strauss. *Deutsche med. Wchnschr.* **39** 1780, 1913.

3 King, G. *Lancet* **1** 385, 1927.

4 Seegen. *Zentralbl. f. d. Med. Wissensch.*, 1884, p. 753. Kulz. *Ztschr. f. Biol.* **27** 228, 1884. Rosin and Laband. *Ztschr. f. klin. Med.* **47** 182, 1902. Schlesinger. *Arch. f. exper. Path. u. Pharmacol.* **50** 1, 1903. Lepine and Boulud. *Rev. de Med.* **24** 185, 1904. Neubauer. *München med. Wchnschr.* **2** 1525, 1905. Moraczewski. *Ztschr. f. klin. Med.* **64** 503, 1907. Adler. *Arch. f. d. ges. Physiol.*, vol. 139, p. 93. Strouse, S., and Friedman, J. C. *Levulosuria*, *Arch. Int. Med.* **9** 99 (Jan.) 1912. Barrenscheen. *Biochem. Ztschr.* **127** 222, 1922. Snapper, I., Grunbaum, A., and van Creveld, S. *Nederl. Tijdschr. v. Geneesk.* **1** 1600, 1926, also, *Arch. f. Verdauungskr.* **38** 1, 1926. Steinberg, S., and Elberg, W. *Klin. Wchnschr.* **4** 2399, 1925.

5 Barrenscheen and Snapper, Grunbaum and van Creveld (footnote 4).

other carbohydrates (for example, cane sugar), is taken up with the food. If the food is totally deprived of this sugar, its excretion at once ceases. This anomaly, in which fructosuria is the only phenomenon distinguishing the patient from a normal person, should not be called a disease. This metabolic deviation may even go on for years, without unpleasant or disastrous consequences (Adler<sup>6</sup> described the case of a patient, aged 73), so that the prognosis is favorable. In some cases, a familial tendency has been described, in others, this factor was absent. If treatment is desired, it is, as already stated, sufficient to omit from the diet all foodstuffs containing fructose, and equally so those carbohydrates from which, in the intestine, fructose is formed, while other carbohydrates are allowed as desired.

To find out to which group our patient belonged, we had to determine first of all whether the function of the liver was normal. The

TABLE 1—*Estimation of Liver Function by Galactose Test*<sup>\*</sup>

Time	Blood Sugar, per Cent	Reduction in Urine
Fasting	0.081	0
After ½ hour	0.095	—
After 1 hour	0.092	0
After 1½ hours	0.097	—
After 2 hours	0.089	0

\* 40 Gm of galactose by mouth

TABLE 2—*Results of Administration of Fifty Grams of Dextrose by Mouth*

Time	Blood Sugar, per Cent	Glycosuria
Fasting	0.079	0
After ½ hour	0.089	0
After 1 hour	0.125	0
After 1½ hours	0.089	0
After 2 hours	0.082	0

usual methods of physical examination did not give any indication of a damaged function (no enlargement of the organ, no splenomegaly, no jaundice or no increased urobilinuria). Moreover, the liver function was estimated by the galactose test, the results of which are given in table 1.

The urine, voided after one and two hours, did not reduce the solutions. After the administration of 50 Gm of galactose by mouth, a feebly dextrarotatory urine was excreted with slightly reducing properties and containing at the most 0.34 Gm of galactose, a quantity undoubtedly to be regarded as entirely normal. We may therefore assume that in our patient the liver function was sufficient.

Secondly, it was necessary to determine whether this fructosuria was not an accompanying symptom of true diabetes mellitus. The blood sugar during fasting appeared to be entirely normal, equally so the blood sugar curve obtained according to Maclean's technic

The alimentary hyperglycemia after the administration of 50 Gm of dextrose by mouth was particularly low, while the fasting level was reached within the normal time. Even after the administration of 100 Gm of dextrose by mouth, the rise in blood sugar was not higher than 0.157 per cent, thus relatively low (table 3).

The decline was somewhat slower after 100 Gm of dextrose had been given, not until after three hours was the fasting level reached. In our case (patient weighing 61 Kg), 100 Gm of dextrose (i.e., 1.6 Gm per kilogram of body weight) was a rather large quantity, so that any disturbance of dextrose metabolism could be excluded.

After proving that there was no disturbance of liver function and no diabetes mellitus, we can safely say that our case belongs to the rare group of cases of essential fructosuria. To understand this peculiar anomaly, one must first consider what happens in the normal organism when fructose is administered.

TABLE 3—Results of Administration of One Hundred Grams of Dextrose by Mouth

Time	Blood Sugar, per Cent	Glycosuria
Fasting	0.091	0
After ½ hour	0.143	0
After 1 hour	0.157	0
After 1½ hours	0.131	0
After 2 hours	0.130	0
After 2½ hours	0.106	0
After 3 hours	0.096	0

Large quantities of fructose may be taken by mouth without a trace of this sugar appearing in the urine. There is, however, a marked difference between the effects from the ingestion of dextrose and of fructose, namely, with fructose there is no increase in the blood sugar. But it is quite certain, that after administration of fructose a slight fructosemia occurs (Isaac<sup>7</sup>, Folin and Berglund<sup>8</sup>).

It is also certain that the liver plays the most prominent part in the storage and transformation of fructose. Isaac<sup>9</sup> discovered that only the unimpaired liver cell is capable of transforming fructose into dextrose (perfusion experiments), while muscles, like the liver, may cause fructose to disappear (glycogenesis, other chemical transversions, combustions, perhaps), but in this case there was no formation of dextrose. Like Folin and Berglund, Isaac believed that the liver cannot store all fructose and that a part escapes into the blood stream and immediately is stored in the muscles. This occurs more rapidly and more completely with fructose than with dextrose, since in the muscles there is a "vacuum" for fructose, while dextrose is always present.

7 Isaac, S. Med Klin 16:1207, 1920.

8 Folin and Berglund. J Biol Chem, vol 51, p 213.

9 Isaac. Ztschr f phys Chem 89:78, 1914.

The normal organism does not excrete fructose in the urine, although after the administration of fructose by mouth, this sugar in low concentration appears in the peripheral circulation (according to Isaac, from 0.02 to 0.04 per cent). So in human beings there is a threshold value for fructose, the height of which is unknown.

Contrary to what we found in man were the results of the perfusion experiments by Hamburger and Brinkman<sup>10</sup> with frog kidneys. These showed that fructose quantitatively passed over from the perfusion liquid into the artificial urine.

To recall the results obtained by various experimenters with the intravenous administration of fructose in man and animals is confusing. If large quantities of fructose are introduced in this manner, it appears that as great a quantity is excreted by the kidneys as is obtained from a solution of dextrose of the same concentration. This becomes evident from experiments by Wierzuchowsky<sup>11</sup> undertaken for different purposes. About 10 per cent of both sugars was recovered in the urine, while after the infusion of dextrose the rise in blood sugar was much higher than that after the introduction of fructose. Here it becomes strikingly apparent how deficient is one's knowledge of the fate of the various carbohydrates in the body. One imagines that the liver, the muscles and the kidneys behave differently toward fructose than toward dextrose, and yet it is a fact that both sugars in almost perfect correspondence are excreted by the kidneys after intravenous administration. There are so many unknown factors that any explanation so far does not seem more than speculation. Owing to the excellent cooperation of our patient, not only did we succeed in being able to confirm the results obtained by other students of this subject, but we were able also to open up some new vistas, which we believe to be of some importance for a better understanding of this abnormal condition.

#### EXPERIMENTS

We will now report the results of various experiments performed on our patient.

The amount of sugar in the blood was determined by the modified micromethod of Bang. In most cases, determinations of fructose in the urine were made as well with the polarimeter as with the reduction method of Causse and Bonnans.

On a mixed diet, our patient always excreted a certain quantity of fructose. This excretion ceased at once if all foodstuffs containing fructose were omitted.

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<sup>10</sup> Hamburger and Brinkman. *Proc. Roy. Acad.*, 1918, vol. 21.

<sup>11</sup> Wierzuchowsky. *J. Biol. Chem.*, vol. 68, p. 631.



Fructose was administered by mouth, as follows 50 Gm of fructose was given on an empty stomach The urine was examined every half hour, and the blood sugar every fifteen minutes during the first half hour, and then every half hour, the results are given in table 4

The same experiment in a normal woman yielded the results shown in table 5

Contrary to what is normally seen, the administration of fructose caused a significant increase in blood sugar, which reached its maximum after one hour, returning to the fasting level after two and a half hours

TABLE 4—*Results of the Administration of Fifty Grams of Fructose by Mouth in Our Patient*

Time	Blood Sugar, per Cent	Fructosuria		
		Polarimeter, per Cent	Polarimeter, Gm	Reduction, Gm
Fasting	0.094	0	0	0
After ¼ hour	0.107	—	—	—
After ½ hour	0.116	0.8	0.26	0.30
After 1 hour	0.144	3.9	1.22	1.24
After 1½ hours	0.123	4.5	1.43	1.51
After 2 hours	0.110	2.8	1.74	1.80
After 2½ hours	0.091	1.6	0.60	0.62
After 3 hours	0.096	0.5	0.40	0.42
After 3½ hours	0.095	0.4	0.34	0.27
After 4 hours	0.087	0.2	0.11	0.15
After 4½ hours	0.077	0.1	0.02	—
After 5 hours	0.096	0.1	0.05	0.07
After 5½ hours	0.071	0.2	0.09	—
After 6 hours		0	0	0
Total excretion 6.32 Gm = 12.6 per cent			6.26	6.38

TABLE 5—*Results of the Administration of Fifty Grams of Fructose by Mouth in a Normal Woman*

Time	Blood Sugar, per Cent	Fructosuria
Fasting	0.096	0
After ½ hour	0.103	—
After 1 hour	0.106	0
After 1½ hours	0.107	—
After 2 hours	0.093	0

Fructosuria appeared within the first half hour, i.e., in a period when the rise in blood sugar was still slight (0.023 per cent) It did not reach its maximum until after two hours, when the blood sugar content had been decreasing for a long time, and it still continued for five and a half hours after administration, i.e., for another three hours after the blood sugar level had become normal So we may conclude that in our case there was practically no threshold for fructose, since this substance appeared in the urine when no more than traces could circulate in the blood In this respect, our case differed from that of Barrenscheen,<sup>12</sup> who found a well marked threshold for fructose in his

<sup>12</sup> Barrenscheen (footnote 4)

case We have stated that in normal persons a threshold for fructose must be assumed, though being relatively low, so that in this respect our patient differed from a normal person

In this experiment, the amount of blood sugar was determined only in the fasting condition and after one hour At this time, fructosemia was determined by the method of Jolles (modified by van Creveld<sup>13</sup>) 1 cc blood was mixed with 1 cc of a 4 per cent solution of hydrochloric acid, and then, while it was vigorously shaken, 2 cc of a 5 per cent solution of mercuric chloride was added by drops, this was followed by centrifugation, 1 cc of the supernatant fluid was mixed with 1 cc of a 25 per cent solution of hydrochloric acid This gave rise to a blue color which was compared with a color scale, obtained by adding different quantities of fructose to normal blood

TABLE 6—*Results of the Administration of One Hundred Grams of Pure Fructose by Mouth*

Time	Blood Sugar, per Cent	Fructosuria (Polarimeter)	
		per Cent	Gm
Fasting	0.048	0	0
After 1 hour	0.134	2.7	1.35
After 2 hours	—	4.05	5.06
After 3 hours	—	4.75	2.00
After 4 hours	—	3.51	1.12
After 5 hours	—	4.56	2.46
After 6 hours	—	1.19	0.67
After 7 hours	—	0.65	0.39
After 8 hours	—	0.24	0.18
After 9 hours	—	0.38	0.15
After 10 hours	—	0.11	0.20
After 11 hours	—	0	0
Total excretion			13.58 = 13.58 per cent

We found in the blood after one hour a fructose content of 0.079 per cent The total sugar content at the same moment was 0.134 per cent, which corresponds to a rise of 0.086 per cent (calculated as dextrose) Now, 0.079 per cent of fructose has the same reducing power as 0.073 per cent of dextrose, so that of the total rise of 0.086 per cent, 0.073 per cent may be attributed to fructose, and only the remaining 0.013 per cent the result of dextrose It would seem therefore, that almost the whole rise in blood sugar is due to fructosemia

We further administered 142 Gm of fructose by mouth (2 Gm per kilogram of bodyweight), from which 19.8 Gm, 13.9 per cent, was excreted A repetition of the same experiment gave an excretion of 18.2 Gm, 12.8 per cent

Not only after the administration of relatively large quantities of fructose, but also after minute quantities, fructosuria occurs

Even after the administration of 2 and of 1 Gm of fructose by mouth, reducing substances were found in the urine

That the excretion is independent of the rapidity with which it is taken up by the body became manifest when 50 Gm were administered, not in a single dose, but in divided doses

When fructose was given intravenously instead of by mouth, we obtained the following results

After the intravenous administration of 20 cc of an 8 per cent fructose solution (1.6 Gm), the urine contained fructose for two hours, a total amount of 0.23 Gm, or 14.4 per cent of the injected quantity. From 50 cc of an 8 per cent solution of fructose (4 Gm

TABLE 7—Results of the Administration of Five Grams of Fructose by Mouth

Fructose Given	Fructosuria (Polarimeter)	
	Per Cent	Gm
Time		
Fasting	0	0
After 1 hour	0.25	0.17
After 2 hours	0.65	0.66
After 3 hours	0.17	0.21
After 4 hours	0	0
Total excretion		1.04 Gm = 20.8 per cent

TABLE 8—Results of the Administration of Fifty Grams of Fructose

Fructose Given		Fructosuria (Polarimeter)	
Time	Gm	Per Cent	Gm
9¾ hours	5	0	0
10¼ hours	5		
10¾ hours	5	0.29	0.61
11¼ hours	10		
11¾ hours	10	1.11	0.89
12¼ hours	5		
12¾ hours	10	1.88	2.07
1¾ hours		0.86	1.88
2¾ hours		0.46	0.87
3¾ hours		0.40	0.72
4¾ hours		0	0
Total given	50 Gm	Total excretion	7.04 Gm = 14.08 per cent

of fructose), which we injected intravenously, 0.41 Gm was excreted in the urine (10.2 per cent) in four hours

In two control experiments, we injected 4 Gm of fructose intravenously into normal persons. No urine showing reducing properties was excreted in either case.

Table 9 shows the excretion of fructose in the foregoing experiments, in which fructose had been given in various ways and in different amounts.

If one bears in mind the quantity of fructose appearing in the urine when widely varying quantities of fructose are administered by mouth, our case brings out anew the fact observed by other investigators that, independent of the quantity administered the excreted amount of fructose

represents a fairly constant percentage of the given dose (about 14 per cent) in all cases. On the administration of 5 Gm of fructose the excretion was even greater than after doses of 100 and 142 Gm<sup>14</sup>

It is logical that our next step would be to ascertain whether the excretion of fructose in our patient was influenced by the hormone which for the carbohydrate metabolism is of overwhelming significance namely, insulin. The experiments by Wiezuchowsky brought out that insulin influences only the excretion of dextrose, while the elimination of fructose remains unchanged if both substances are introduced intra-

TABLE 9—Results Obtained from the Administration of Fructose

Method	Fructose Given, Gm	Fructose Excreted	
		Gm	Per Cent
By mouth	10	+	+
By mouth	20	+	+
By mouth	50	1.04	20.80
By mouth	50.0	6.32	12.64
By mouth (in refracted dose)	50.0	7.04	14.08
By mouth	100.0	13.58	13.58
By mouth	142.0	19.00	13.38
Intravenously	16	0.27	14.38
Intravenously	10	0.41	10.20

TABLE 10.—Results of the Administration of Insulin

	Blood Sugar, per Cent	Fructosuria		
		Polarimeter		Reduction Gm
		Per Cent	Gm	
Fasting, 10 units of insulin	0.085	—	—	—
After ½ hour, 50 Gm of fructose by mouth	0.095	0	0	0
After 1 hour	0.122	—	—	—
After 1½ hours	0.123	1.31	2.15	2.21
After 2 hours	0.117	—	—	—
After 2½ hours	0.111	1.37	3.90	4.27
After 3½ hours	0.102	0.51	1.17	1.35
After 4½ hours	0.107	0.40	0.40	0.45
After 5½ hours	0.107	0.14	0.18	0.24
After 6½ hours	0.108	0	0	0
Total excretion	8.16 Gm = 16.32 per cent		7.80	8.12

venously. In perfect harmony with these investigations, in the case of Snapper, insulin did not produce a diminished fructosuria. Table 10 shows that in our case also no action of insulin could be seen.

Earlier observations showed that for the excretion of fructose in persons with fructosuria, it is not immaterial whether the fructose is administered as the only carbohydrate or introduced with other carbohydrates, or whether it is introduced as disaccharide and polysaccharide respectively. Schlesinger and Barienscheen reported that under the

<sup>14</sup> The fructosuria after the administration of 5 Gm of fructose by mouth was different from that in all other similar experiments so we repeated this one with just the same result.

latter conditions more fructose appears in the urine. We gave fructose by mouth in combination with an equal quantity of dextrose and galactose, which are, in contrast to fructose, metabolized in a normal manner. The results appear in tables 11 and 12.

The excretion of fructose was also studied after the administration of 96 Gm of cane sugar (representing 50 Gm of fructose).

Under the conditions represented in table 13, a greater part of the fructose was excreted than when fructose was given alone. It is most remarkable that after the administration of cane sugar the fruc-

TABLE 11—*Results of the Administration of Twenty-five Grams of Fructose and Twenty-five Grams of Dextrose by Mouth*

Fructose Given	Fructosuria (Polarimeter)	
	per Cent	Gm
Fasting	0	0
After 1 hour	0.63	1.25
After 2 hours	0.85	1.62
After 3 hours	0.63	1.25
After 4 hours	0.28	0.93
After 5 hours	0.23	0.41
After 6 hours	0	0
Total excretion		5.46 Gm = 21.8 per cent

TABLE 12—*Results of Administration of Twenty-five Grams of Fructose and Twenty-five Grams of Galactose by Mouth*

Fructose Given	Fructosuria (Polarimeter)	
	per Cent	Gm
Fasting	0	0
After 1 hour	0.57	1.51
After 2 hours	0.80	1.63
After 3 hours	0.34	0.61
After 4 hours	0.20	0.48
After 5 hours	0.06	0.21
After 6 hours	0	0
Total excretion		4.44 Gm fructose, 17.8 per cent

tosuria was considerably greater than when fructose and dextrose were given together.

Of more importance than the fructosuria only is the behavior in regard to inulin, the polysaccharide of fructose. Neubauer demonstrated that this substance was not excreted by his patient with fructosuria, contrary to what had been expected. We obtained the same results. Neither did the patient give a reduction in the urine on the administration of 5 or 20 Gm of inulin. Neubauer pointed out that nothing is known of what happens with the inulin in the intestine. One is inclined to assume that it is converted into fructose, analogous to the breaking up of amylin into dextrose. But this has by no means been proved. On the contrary, many arguments against it may be adduced.

Lewis and Fraenkel<sup>15</sup> found that in dogs in which diabetes has been produced by the administration of phlorizin, an additional amount of dextrose appears in the urine after the administration of fructose, but not following a dose of inulin

Goudbeig<sup>16</sup> did not observe a rise of the respiratory quotient after administering inulin, contrary to the results obtained after giving fructose. The results of Neubauer, corroborated by us, accord perfectly with this. The fact that inulin does not produce fructosuria in a patient who may be regarded as markedly sensitive to fructose is a strong plea for the contention that in the intestine, at any rate, no fructose is formed from inulin.<sup>17</sup>

TABLE 13—Results of the Administration of Ninety-Six Grams of Cane Sugar by Mouth

Time	Blood Sugar, per Cent	Fructosuria		
		Polarimeter		Reduction, Gm
		per Cent	Gm	
Fasting	0.058	0	0	0
After 1 hour	0.157	1.43	2.86	2.83
After 2 hours	0.143	2.05	5.14	5.80
After 3 hours	—	1.48	3.25	3.29
After 4 hours	—	2.58	2.85	3.14
After 5 hours	—	1.23	0.68	0.80
After 6 hours	—	0.94	0.32	0.37
After 7 hours	—	0.28	0.14	0.16
After 8 hours	—	0	0	0
Total excretion 15.81 Gm = 31.6 per cent			15.24	16.39

The metabolic disturbance in our patient was concerned only with fructose, while dextrose, galactose and mannose were assimilated in a normal manner.

A glance at the structural formula of fructose will reveal that it occupies a place by itself. It is a ketose, while the other sugars are aldoses.

#### Structural Formulas

H	H	H	H
H-C-OH	H-C-OH	H-C-OH	H-C-OH
H-C-OH	H-C-OH	HO-C-H	H-C-OH
H-C-OH	H-C-OH	H-C-OH	H-C-OH
HO-C-H	HO-C-H	H-C-OH	HO-C-H
H-C-OH	HO-C-H	HO-C-H	C=O
C=O	C=O	C=O	H-C-OH
H	H	H	
Dextrose	Mannose	Galactose	Fructose

<sup>15</sup> Lewis and Fraenkel J Biol Chem, 1914, vol 17

<sup>16</sup> Goudberg Ztschr f exper Path u Therap, vol 13, p 310

<sup>17</sup> We could prove the absence of inulin in the urine by finding no reduction on heating in an alkaline medium reaction, by which inulin is easily broken up into fructose.

It is desirable to determine whether the disturbance is due to this difference in structure, that is, whether it depends on the presence of the keto-group. It happens that almost all sugars in nature are aldoses, there being only three known ketoses

H	H	H
H-C-OH	H-C-OH	H-C-OH
H-C-OH	HO-C-H	H-C-OH
H-C-OH	H-C-OH	HO-C-H
HO-C-H	HO-C-H	HO-C-H
C=O	C=O	C=O
H-C-OH	H-C-OH	H-C-OH
H	H	H
Fructose	Sorbose	Tagatose

Tagatose is a sugar rarely encountered and difficult to prepare. We did not succeed in procuring it. Sorbose is not so rare. It is prepared from the fruit of rowan (*Sorbus aucuparia*). It is levorotatory, and gives, like fructose, the reactions of Selwanoff and Bang, but does not ferment, by which characteristic it can be differentiated from fructose. Owing to the kindness of Professor Boeseken at Delft, we obtained about 5 Gm of this hexoketose. We administered 4.8 Gm in one dose.

TABLE 14—Results of the Administration of 4.8 Gm of Sorbose by Mouth

Time	Blood Sugar, per Cent	Sorbosuria		
		Polarimeter		Reduction, Gm
		per Cent	Gm	
Fasting	0.085	0	0	0
After ½ hour	0.087	—	—	0.11
After 1 hour	0.086	0.88	0.68	0.55
After 1½ hours	0.093	0.54	0.86	0.81
After 2 hours	0.086	0.54	0.54	0.40
After 2½ hours	0.079	0.38	0.30	0.34
After 3 hours	0.076	0.38	0.21	0.23
After 3½ hours	—	0.50	0.25	0.28
After 4 hours	0.093	0.50	0.33	0.25
Each half hour until after 7 hours	—	0.25	0.50	0.65
After 7½ hours	—	0	0	0
Total excretion 3.65 Gm sorbose = 76 per cent			3.67	3.62

The patient appeared to be much more sensitive to sorbose than to fructose. No less than 76 per cent of the administered quantity was recovered in the urine as sorbose, as the negative fermentation test showed.

Our supply was too small for a study of the tolerance of healthy persons, and we must, therefore, rely on the literature on this subject, which from its very nature is meager. Of 3 Gm of sorbose given by mouth, Cremer<sup>18</sup> could recover 17 per cent in the urine, while after the ingestion of 0.25 Gm and 1 Gm, respectively, no reduction was obtained.

<sup>18</sup> Cremer Ztschr f Biol 29 484, 1892

Voit<sup>19</sup> obtained 36 per cent in the urine, after injecting 10 Gm subcutaneously. From these figures, and in the absence of other data, we believe the excretion is so much higher than the amount mentioned by the investigators that we feel justified in speaking of an abnormal reaction in our patient toward sorbose. We, therefore, hold that this result, if corroborated by the necessary control tests in healthy persons, may serve as argument for the contention that the presence of the keto-group is of predominating significance for the special place fructose holds among the other sugars studied.

Besides sorbose, we also studied dioxy-acetone,  $\text{CH}_2\text{OH}-\text{CO}-\text{CH}_2\text{OH}$ , equally a ketose. Our patient, as well as healthy persons, did not excrete this substance in the urine. It is well known that this sugar is much more easily stored by the liver (as glycogen) than all other known higher sugars (Isaac and Adler<sup>20</sup>).

It is not permissible to place this keto-triose on a level with the higher ketoses, and so we must abstain from any conclusion in this respect.

Where in the body is the seat of the metabolic disturbance found, and what is its underlying mechanism?

As to the location of the disturbance, one thinks, first of all, of the organ which, under normal conditions, has the greatest influence on fructose metabolism—the liver. The fact that the administration of fructose by mouth leads to a considerable degree of fructosemia is a strong argument for the assumption that the liver allows more fructose to escape into the blood stream under these circumstances than under normal conditions. A disturbed flow from the circulation toward the muscles (Folin and Berglund) might be considered, but this is a purely hypothetical notion. It is contrary to the facts to assign to the muscles, instead of the liver, a preponderating influence on fructose metabolism, as investigations by Isaac and others have brought out.

A more positive proof that the liver is the primary seat of the disturbance is the fact that the fructosuria is just the same whether fructose is administered by mouth or intravenously. From this we may infer that the influence of the liver on the storing of fructose is extremely slight, contrary to the tendency in normal persons.

It is more difficult to explain the mechanism of this disturbance. In the first place, one must bear in mind the remarkable constancy of the fructose excretion when greatly varying doses are administered. This phenomenon cannot be accounted for by the assumption that there is an insufficiency of a definite function, as in diabetes mellitus. In the latter condition, different quantities would be excreted not only in the

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19 Voit. *Deutsches Arch f klin Med* 58 535, 1897

20 Isaac, S., and Adler, E. *Klin Wchnschr* 3 1208, 1924



same patient, but in different cases. The fact that always the same fraction of the introduced fructose is excreted indicates with certainty that a definite metabolic function has dropped out.

There are two possibilities to be thought of, as Neubauer lucidly reasoned out, but later investigators have paid little attention to them. However scant our knowledge of the normal fructose metabolism may be, it is certain that the greater part of the fructose which the liver gets from the intestine is stored in that organ as glycogen, and that a smaller part passes over into the blood stream, from which it disappears rapidly. We also know that a part of the fructose is at once oxidized. This oxidation process is manifested by a rapid increase in the excretion of carbon dioxide, together with a rise of the respiratory quotient, a phenomenon repeatedly observed.

Neubauer suggested that the disturbance is possibly this: under normal conditions, a definite part is always oxidized, but in patients with fructosuria this oxidation process fails. Neubauer himself had no opportunity to determine the amount of carbon dioxide excretion. We determined the respiratory quotient in our patient twice before, and one hour after, the administration of 142 Gm of fructose (2 Gm per kilogram of body weight), with the following results:

	Respiratory Quotient Before	Respiratory Quotient After
Normal person	0.71	0.95
Our patient, first test	0.72	0.77
Our patient, second test		0.75

Here one sees striking evidence that a rise in the respiratory quotient, as compared with what is observed in normal persons, is absent, and we may conclude, therefore, that no combustion of sugar takes place.

In a return again to the constant relation between the fructose administered and that excreted, which in all observed cases of fructosuria is of the same value, the question arises whether an analogy is found somewhere else.

Hamburger,<sup>21</sup> in his experiments on the permeability of the glomerulus membrane to stereo-isomeric sugars, found a similar phenomenon. On perfusion of the frog's kidney with Ringer's solution to which various sugars had been added, it was shown that galactose was partially retained. Closer investigation into the permeability of galactose showed that independent of the concentration of the galactose in the perfusion fluid, there is always a fairly constant part, namely, the lesser half, that is passing through. The same occurrence was revealed on perfusion with levoxyllose. At once we were impressed by the analogy between

21 Hamburger Biochem Ztschr 128 185, 1922

the results of these perfusion experiments and what we found in fructosuria Hamburger looks for an explanation in the different behavior of the two forms, the  $\alpha$ —and  $\beta$ —modification, which together, as equilibrium mixture, form the d-galactose

From the rotation coefficients of the two forms, their mutual relation may be calculated, and it is shown that the excreted part of galactose corresponds nicely to the quantity of one of the forms

With regard to fructosuria, we have suggested the possibility that the body is abnormally adapted to one of the two modifications of fructose, and that the organism is not capable of assimilating it in the normal manner This modification may have a constant value in the equilibrium between the two

If from the rotation of the two separate forms and the equilibrium one calculates the relation between the  $\alpha$ —and  $\beta$ —modification, one finds 37 per cent  $\alpha$ -fructose and 63 per cent  $\beta$ -fructose The amount excreted by our patient (approximately 14 per cent) can, therefore, not be held to consist of only one of the two forms However, the possibility must be borne in mind that in vivo the equilibrium is different from that in an aqueous solution, on which our calculations are based We did not succeed in finding in Ringer's solution a rotation differing from that in water, but in vivo there may be various known and unknown factors that influence this equilibrium Above all, it should not be forgotten that Hamburger made his perfusion experiments with surviving frog kidneys, whereas we dealt with the complete living human organism

For the present, no further advance is to be made from mere theoretical speculation We have, nevertheless, attempted by experimental methods to prove the probability that the mystery of the constant excretion is connected with the equilibrium between the  $\alpha$ - and  $\beta$ -fructose

If fructose as solid substance (i.e.,  $\beta$ -fructose) is dissolved,  $\alpha$ -fructose in the increasing quantities gradually arises in the solution until after a time equilibrium is established This phenomenon can be controlled by the polarimeter, rotation of the solution diminishes (so-called multirotation)

We injected intravenously a solution of fructose immediately after its preparation and observed the excretion A considerably greater part of the fructose appeared in the urine than after the intravenous administration of a solution of fructose dissolved some time prior to injection On the administration of fructose by mouth, no marked difference is to be expected, since with fructose the equilibrium is established rather quickly (within a half hour), so that when absorption from the intestine is complete, equilibrium has already been established This observation can be explained only by the assumption that the disturbance found in our patient is bound up with one of the two modifications

There is a second argument, pointing in the same direction, namely, that the excietion of the fructose depends on the simultaneous presence of other sugars. It is plausible that under those conditions other equilibriums arise than with fructose alone. The same holds good for cane sugar, from which fructose is not formed until it has reached the gastro-intestinal tract.

With the same question in view, we finally introduced crystalline fructose through the rectoscope as high into the rectum as possible. Of 17.5 Gm., 7.7 Gm. (44.4 per cent) was excreted with the urine.

This is a considerable difference, but we do not believe it to be of great importance on account of the manner in which the fructose was introduced. Theoretically, there is considerable indication in the results of our experiments that the metabolic disturbance in fructosuria is particularly associated with one of the two forms of fructose.

TABLE 15—*Results of the Intravenous Injection of 7.7 Gm. of a Solution of Fructose Immediately After It Was Prepared*

Time	Fructosuria	
	Polarimeter, Gm.	Reduction, Gm.
Fasting	0	0
After ½ hour	0.89	0.92
After 1 hour	0.28	0.23
After 1½ hours	0.13	0.13
After 2 hours	0.06	∞
From 2½ until 5 hours	0.16	0.12
After 5½ hours	0	0
Total excretion 1.46 Gm. = 19 per cent	1.52	1.40

It would be of great interest to examine the urine immediately after its formation in the kidneys with regard to the phenomenon of multi-rotation. We did not consider ourselves justified in carrying out the necessary cystoscopy and ureteral catheterization.

We saw that not only fructose, but also sorbose, is excreted for the greater part with the urine of our patient, and that from the literature it is known that this rare sugar is the only one of all known sugars that, when ingested by normal persons, passes over into the urine. We believe that a more profound investigation of the manner in which the excretion takes place, and, in particular, a quantitative examination under varying conditions might lead to important results. The difficulty in obtaining a sufficient quantity of sorbose is the only obstacle.

In our patient, the fructosuria was encountered as an isolated metabolic disturbance, since, apart from a mild pulmonary tuberculosis, she did not show any pathologic anomaly. She did not present any other sign of constitutional deficiency, nor of disturbance in the organs of internal secretion, as has been reported by other investigators in similar cases. Mentally she was entirely normal. Hereditary tendencies were

totally absent and, so far as known, there were no other cases of fructosuria in her relatives. Of her near relatives (father, mother, brother and sister), we had the opportunity to examine the urine voided after the ingestion of a fairly large quantity of cane sugar. Reducing substances were not found. Cases of diabetes mellitus or of other disturbances of metabolism were not encountered in the relatives. So there was nothing in our case pointing to an hereditary constitutional anomaly. Nevertheless, on the ground of other cases reported in the literature, we have to assume such a constitutional factor.

Of great interest is the idea of van Creveld, who suggested the possibility of the fructosuria being a remnant of fetal life. He found that new-born children, particularly premature children, have less tolerance to fructose. This tolerance of fructose, according to him, develops slowly during fetal life, and if it does not arise, fructosuria results.

When the function of the liver is otherwise intact, a partial decrease in tolerance to fructose is never met with (that is, a true fructose-diabetes), but either a normal reaction toward this sugar or the typical picture of fructosuria. This fact, we believe, speaks strongly against van Creveld's hypothesis.

Resuming, we find that fructosuria is, from many points of view, a remarkable disturbance of metabolism, though harmless in character.

That so far our insight into the essential nature of this condition is but dim is, in the first place, due to the great rarity of the anomaly. But when we have the opportunity, with the complete and admirable cooperation of the patient, to examine such a case, we are, in our attempts at interpreting the results of various experiments, continually handicapped by the great gaps in our knowledge of the normal metabolism of fructose. Notwithstanding, we do believe that our observations have shed more light on a few points thus far in utter darkness.

#### SUMMARY

An extensive investigation was made in a case of true (essential) fructosuria, and the following facts were determined:

1. Fructosuria disappears at once, if only food, free from fructose is consumed.
2. Independent of the quantity of fructose administered, a fairly equal part of it is excreted by the urine (about 14 per cent).
3. Contrary to the results under normal conditions, the administration of fructose leads to a considerable rise of the blood sugar content due almost entirely to fructosemia.
4. After the administration of fructose in divided doses as much is excreted as when fructose is given in a single dose.

5 The intravenous introduction of fructose produces fructosuria of the same degree as administration by mouth

6 Insulin has no influence on the fructosuria

7 Fructose, given in combination with other sugars or as a polysaccharide, results in a more severe fructosuria than when nothing else is given

8 Inulin does not produce fructosuria, probably because it is not broken up in the intestine into fructose

9 The metabolism of dextrose, galactose, maltose and mannose is not disturbed

10 Sorbose (a ketose like fructose), the only known sugar that is normally excreted in small quantities in the urine, was excreted in large quantities in the urine in our case. The keto-group was probably responsible for this metabolic disturbance

11 After the administration of fructose, there is no rise of the respiratory quotient, contrary to what is seen in normal conditions

12 Fructose injected into the vein immediately after the solution has been prepared leads to a greater degree of fructosuria than the intravenous introduction of a solution prepared some time prior to the injection

13 Crystalline fructose, administered by rectum, produces a more severe fructosuria than fructose given by mouth

14 A connection probably exists between the last two results (nos 12 and 13) and the phenomenon of mutarotation

# HYPERINSULINISM

## REPORT OF TWO CASES <sup>†</sup>

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Since the introduction of insulin in treatment, the symptoms of hypoglycemia have become well known. Many cases are being recognized in which hypoglycemia occurs spontaneously. As a rule, the symptoms are mild, but in a small number of cases they have been severe. The increasing incidence of the disorder and the serious disability which sometimes results make careful investigation highly important.

## REPORT OF CASES

Three cases in which there was a constant tendency to severe hypoglycemia have been observed at the Mayo Clinic. I reported the first case (case 1) about two years ago in collaboration with Wilder, Power and Robertson <sup>1</sup>. The patient had attacks of loss of consciousness with convulsions, if he failed to receive sugar every hour during the day and night. It was demonstrated that hypoglycemia was due to overproduction of insulin from carcinoma of the islands of the pancreas.

CASE 2—A farmer, aged 52, came to the Mayo Clinic in August, 1928, because of attacks of weakness and stupor which had occurred at intervals for more than two years. On many occasions he had lost consciousness and had had convulsions. He noted that the attacks were most likely to occur if he had gone without food for several hours, or if he undertook any exertion. He found that eating would relieve or prevent the symptoms, so he formed the habit of taking food at frequent intervals. A curious incident in the history is that early in the course of the trouble he fell into a stuporous state which persisted for a week. Because a trace of sugar had been found in the urine previously, diabetic coma was suggested, although glycosuria was not observed at this time. Insulin was given for ten days, probably in small doses. The patient was able to swallow liquid nourishment such as eggnog and orange juice, and was fed liberally. He regained consciousness gradually. As time went on, the patient had to take larger amounts of food at shorter intervals. For several months before admission, he had been obliged to eat at bedtime and during the night. He was unable to work, slight exertion, such as mowing his lawn, often precipitated attacks. Even when resting failure to take sufficient food resulted in attacks several times a week. The patient's condition was considered hopeless.

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<sup>†</sup> Read before the Central Society for Clinical Research, Chicago, Nov 23, 1928. The work was done in the Division of Medicine, the Mayo Clinic.

<sup>1</sup> Wilder, R M, Allan, F N, Power, M H, and Robertson H E. Carcinoma of the Islands of the Pancreas, Hyperinsulinism and Hypoglycemia, J A M A 89 348 (Jul 30) 1927

Investigation showed that when food was withheld, there was a gradual fall in the level of the blood sugar. If it fell below 0.06 per cent, the usual symptoms of hypoglycemia appeared. The lowest amount of blood sugar observed was 0.04 per cent. To prevent hypoglycemia, food with the equivalent of 500 Gm of dextrose each day was required, lunches being given between meals and three times during the night. The injection of epinephrine hydrochloride caused a rise in blood sugar, and relief of symptoms. Solution of pituitary had a similar influence, although it was less powerful. Atropine did not have any effect. A diagnosis of hyperinsulinism was made because of the resemblance of this case to case 1. The condition could not be controlled by medical measures, and since the patient was incapacitated the decision was made to resort to surgical procedures. It was hoped that a localized tumor might be found in the pancreas, the removal of which would cure the patient.

The operation was performed Sept. 12, 1928 (Judd). The pancreas and neighboring organs appeared normal. The tail of the pancreas and part of the body were resected. The portion removed weighed 14 Gm. Microscopic examination did not show visible abnormality.

After the operation, the tendency to hypoglycemia had apparently disappeared. On the second day on which no sugar or other nourishment was given, the blood sugar varied between 0.114 and 0.075 per cent. The usual postoperative feeding was commenced on the third day. Two weeks later, when food with the equivalent of 200 Gm of dextrose was taken in twenty-four hours, the blood sugar values were subnormal, approximately 0.06 per cent, in the morning. The amount of food was, therefore, increased.

It was apparent that the tendency to hypoglycemia had not been completely abolished, but had been decidedly decreased. The patient was finally able to live on only three meals a day and without taking nourishment during the night. He returned to his home on October 25. Weekly reports show that mild hypoglycemic symptoms have occurred a few times only.

**CASE 3**—A man, aged 47, came to the clinic in October, 1928, because of symptoms similar to those in cases 1 and 2, they had first appeared four years before and had gradually increased in severity. Three years before admission, disturbances of sleep and somnambulism appeared, two years before, a violent convulsive attack occurred during the night. He noticed that eating relieved the symptoms or checked the attacks, so that he began to take food three times during the night as well as between meals. In spite of precautions, attacks of weakness and stupor occurred with increasing frequency, especially after exertion, and he was obliged to give up his work. About two months before admission, he was in a hospital, where food was not given after 5.30 p. m. Attacks occurred during the night, in which he became irrational and maniacal so that he was confined in a straight-jacket on several occasions. Recovery occurred spontaneously after several hours.

Examination of the blood showed that the sugar content fell when food was not taken, sometimes reaching 0.04 per cent. Hypoglycemic symptoms usually appeared when the blood sugar fell below 0.05 per cent. The ingestion of food with the equivalent of from 400 to 450 Gm of dextrose prevented hypoglycemic symptoms when given at suitable intervals. Epinephrine and solution of pituitary showed transitory effects in checking hypoglycemia. Ephedrine also appeared to have some influence. The patient is still under observation.

## COMMENT

The symptoms of hypoglycemia are remarkable in their variation, but are not difficult to recognize. The characteristic feature is the prompt relief which follows the ingestion of sugar or other carbohydrate food. Each of these patients had learned by his own experience that he could avoid or check his symptoms by eating at frequent intervals. The suggestion given by this history can readily be verified by the blood sugar test.

Although hypoglycemia can be recognized with ease, determination of the exact cause is difficult. Theoretically, the primary factors may be either failure of the liver or overfunction of the pancreas. Although the removal of the liver from an animal results in immediate fall in blood sugar, on only rare occasions has hypoglycemia been observed in cases of definite hepatic disease. These have been cases of advanced cirrhosis, acute yellow atrophy or extensive tumors of the liver. In the presence of such gross disturbances, one may feel satisfied that hypoglycemia, if present, is of hepatic origin. In most cases of spontaneous hypoglycemia, direct evidence of hepatic disorder is not manifested. Yet it is possible that the liver may still be at fault. It is conceivable that one function may fail, although other functions are intact. Unfortunately, there is no method which adequately tests the function of the liver with respect to carbohydrate metabolism.

The possibility of hyperinsulinism was first suggested by Harris<sup>2</sup> who described several cases in which slight hypoglycemia and mild symptoms were present. Not until the report of our first case was a definite pathologic basis demonstrated for this previously hypothetical condition. Since then hyperinsulinism has been recognized in two other cases of tumors of the pancreas. In one of these cases, reported by Thalhimer and Murphy,<sup>3</sup> necropsy revealed a nodule in the pancreas with groups of tumor cells identical in appearance with normal islands of Langerhans. In the other case, McClenahan and Norris<sup>4</sup> also found an adenoma of island tissue. The clinical picture of tumor of the islands of the pancreas with overproduction of insulin is now established as a disease entity as Wilder<sup>5</sup> has indicated.

The condition encountered in case 2 seems to indicate that hyperinsulinism may also exist without any anatomic change of the pancreas.

2 Harris, Seale. Hyperinsulinism and Dysinsulinism. *J. A. M. A.* **83**: 729 (Sept. 6) 1924.

3 Thalhimer, W., and Murphy, F. D. Carcinoma of the Islands of the Pancreas, Hyperinsulinism and Hypoglycemia. *J. A. M. A.* **91**: 89 (July 14) 1928.

4 McClenahan, W. U., and Norris, W. G. Pancreatic Adenoma with Hypoglycemia. *Am. J. M. Sc.*, to be published.

5 Wilder, R. M. Tumor der Langerhansschen Inseln mit Hyperinsulinismus, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **40**: 223, 1928.



A similar case was reported by Finney and Finney,<sup>6</sup> who were the first to attempt surgical treatment of this condition. Their patient had suffered from spells of mental confusion and peculiar behavior for four years, with decreases in the blood sugar to as low as 0.03 per cent. At operation the pancreas appeared normal. Following the removal of a portion weighing 22.5 Gm., the tendency of the blood sugar content to fall below normal was checked for several days. Later, hypoglycemic symptoms appeared, although apparently they were not as severe as before. In such cases, overproduction of insulin may depend on stimulation by nervous mechanism or some other cause. That the disorder may exist without visible abnormality is not surprising, since the opposite condition, diabetes, may likewise occur without visible change in the islands of Langerhans.

Direct proof that hyperinsulinism actually exists in cases 2 and 3 cannot be furnished. There is no satisfactory method of assaying the insulin in the blood. In the cases of tumors of the pancreas, the rôle of the pancreas was demonstrated positively only by surgical exploration or by necropsy, yet it is possible that the clinical differentiation of hyperinsulinism and selective hepatic insufficiency may be made by indirect methods. Epinephrine and solution of pituitary do not affect the blood sugar of a dehepatized animal. The rise in blood sugar content following the administration of these agents might, therefore, be taken as evidence that in cases 2 and 3 the hypoglycemia was not due to loss of hepatic function. In case 1, epinephrine and solution of pituitary did not have any effect, presumably because of the overwhelming amount of insulin in the body. Here the amount of sugar required to prevent hypoglycemia may help in the diagnosis. Mann and his coworkers found that a dehepatized dog requires from 0.25 to 0.5 Gm. of dextrose for each kilogram of body weight each hour to maintain the blood sugar level. The calorie equivalent of the maximal requirement is approximately equal to the basal heat production. One might assume that the loss of hepatic function in man would create a demand for a corresponding amount of sugar. Therefore, if the calorie equivalent of the sugar required to prevent hypoglycemia in a man at rest were much in excess of the basal heat production, it might indicate that sugar was required not merely to compensate for loss of hepatic function, but to meet the demand for increased utilization due to insulin. Using a rough calculation and assuming that the average basal heat production of a man is 1 calorie for each kilogram each hour, one might conclude that if more than 0.25 Gm. of sugar for each kilogram of body weight each hour

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<sup>6</sup> Finney, J. M. T., and Finney, J. M. T., Jr. Resection of the Pancreas, *Ann. Surg.* 88: 584, 1928.

were required, hypoglycemia must be due to hyperinsulinism. In case 1, approximately twice this amount was eventually needed. In cases 2 and 3, the amount of sugar needed was not great enough to make this criterion applicable. Yet in each of the three cases the diagnosis of hyperinsulinism seemed logical.

The psychiatrists who observed the case reported by Finney and Finney suspected hysteria, and the failure of the operation to give complete relief apparently led to the conclusion that "the spells are wholly psychogenic in origin." No doubt, in many such cases the patients are dismissed with this diagnosis. Other cases probably are diagnosed as epilepsy. However, when blood sugar determinations show that the symptoms are invariably associated with hypoglycemia and that immediate relief follows elevation of the blood sugar, the diagnosis of hysteria or neurasthenia is dangerous. It can be recalled that the nervous manifestations of hyperthyroidism were often attributed to neurosis.

The obvious treatment of hyperinsulinism is to provide sugar, or other carbohydrate food, in sufficient amounts and at the proper time to maintain the blood sugar level. If the symptoms are mild, this might be done without difficulty, but in the cases described, even with the knowledge of the remedy, it has been impossible for the patients to lead a normal existence. Unusual exertion or failure to take sufficient food precipitated loss of consciousness, and unbroken sleep was impossible. Medical measures have been of little value. Epinephrine hydrochloride, solution of pituitary and ephedrine have only transitory effects. Because of the analogy of the condition to hyperthyroidism, as pointed out by Wilder,<sup>5</sup> surgical measures appear to offer the greatest benefit. In cases of hyperinsulinism due to a localized tumor, complete cure should follow excision. Overactivity of the whole gland which probably existed in the two cases in which operations were performed is, naturally, more difficult to remedy. In neither case was complete relief obtained, but in one case the improvement was considerable.

#### SUMMARY

Hyperinsulinism due to overproduction of insulin from a tumor of the islands of the pancreas is now established as a disease entity. It is probable that hyperinsulinism may also be due to a functional disturbance of the pancreas. The differential diagnosis of hypoglycemia due to hyperinsulinism and hypoglycemia due to selective hepatic insufficiency is a difficult clinical problem. Two criteria may have value in differentiation: the effect of epinephrine hydrochloride and solution of pituitary, and the amount of sugar required to maintain the blood sugar level. When the hypoglycemic tendency is so strong that the patient is incapacitated, surgical treatment appears to promise relief.

Three cases are described in which there was a constant tendency to severe hypoglycemia attributed to hyperinsulinism. In case 1, there was a carcinoma of the islands of Langerhans. In case 2, surgical exploration revealed a normal appearing pancreas. Resection of a part of the pancreas was followed by considerable relief. In case 3, in which medical treatment alone was given, the patient is still under observation.

# AN IMPROVED DUODENAL TUBE

## ITS ADVANTAGES, WITH A BRIEF OUTLINE OF DUODENAL INTUBATION <sup>†</sup>

C VICTOR RICHARDS, M D  
BALTIMORE

Nonsurgical damage of the gallbladder incident to a complete investigation of the gatio-intestinal tract has heretofore required several hours. With the improved tube and altered technic, it requires only one-half hour.

### DESCRIPTION OF THE TUBE

The olive. The fenestrations and lumen are larger, the lumen extending throughout the entire olive, all sharp edges are rounded, polished and gold plated to prevent discoloration and corrosion.

The tube. The overall diameter of the tube and of the olive are thus approximately equal. The proximal end attachments are omitted as unnecessary. An all rubber, 3 ounce syringe with a hard rubber or bakelite cannula is all that is necessary. It facilitates the method of obtaining material for culture.

### TECHNIC

The following is an outline of the technic to be used.

Time. Preferably 9 a. m., on a fasting stomach.

Material.

- (a) Hypertonic solution of sulphate of sodium, magnesium, potassium and calcium warmed.
- (b) Author's modified tube.
- (c) Funnel-shaped cannula to fit the proximal end of the tube.
- (d) Three ounce all rubber syringe.  
The instruments are submerged in a jar of 95 per cent alcohol, they are thoroughly washed, but not boiled.
- (e) Sterile water in 500 cc. flasks covered with 50 cc. jar sterilized daily.
- (f) Sterile large test tube.
- (g) Astringent solution.

Stage I. Position of Patient (Seated or Standing)

- (a) Direct the olive gently to the pharynx, after one swallow the tube may be continued to notch II without any interruption or reflex gagging. Place the patient on the right side, receive the stomach contents by syphonage. Titrate and examine microscopically.
- (b) Wash three times with 500 cc. of sterile water or with some mild astringent.

Stage II

- (a) Advance the tube to notch III. Allow the greater curvature of the stomach to direct the tube into the duodenum. Syphon the duodenal contents, examine microscopically and culture.
- (b) Wash as in stomach method.

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<sup>†</sup> Submitted for publication, Nov. 7, 1928.

\* Read before the Medical and Chirurgical Faculty, Feb. 15, 1928, at Baltimore.

(c) Localize tube

- 1 Observation by injecting air Usually sensations felt above the umbilicus indicate that the tube is in the stomach, if below the umbilicus and more definitely sensed, in the duodenum  
The sound transmission due to the pressure required with air and liquid is distinctly different, being cavernous in the stomach and muffled and distant in the duodenum
- 2 Fluoroscopic localization is never needed

Stage III

- (a) Instil hypertonic solution of from 25 to 50 cc with moderate force, retain until nausea is experienced or until after a five minute lapse of time, then allow to syphon back into the sterile container Bile fractions are obtained as usual
- (b) A test tube of 95 per cent alcohol is sufficient for sterilization of the proximal end of the tube, which can be placed in a sterile test tube to receive the contents for culture
- (c) Wash or instil suitable preferred solutions and withdraw the tube slowly without interruption

ADVANTAGES OF IMPROVED TUBE

The advantages of the new tube are all due to its increased rigidity and diameter Its advantages during administration are as follows

- (a) Swallowing, peristalsis and fluoroscopic localization are unnecessary
- (b) The contents of the stomach, duodenum and gallbladder can be obtained in one-half hour
- (c) The tube does not become knotted

These advantages enable the operator to perform as a routine measure a technic on a patient with that of the examination of the heart, lungs and kidneys

The advantages during the instillation stage are

- (a) The lumen and fenestrations permit the exit of heavy mucus by syphonage alone Essence of caiod is a distinct adjunct when tenacious mucus is encountered
- (b) The fanlike splashing of the duodenal wall by the hypertonic solution provides a larger surface area in stimulating the neuromuscular mechanism incident to drainage of the gallbladder
- (c) Reflex gagging and vomiting are practically negligible, but if they do occur, they do not eject the tube

# TOXIC ADENOMA OF THYROID<sup>1</sup>

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A review of the literature shows that toxic adenoma of the thyroid has been considered under a variety of names. Some of these synonyms are

Enlargement of the thyroid gland in connection with enlargement or palpitation of the heart—Parry<sup>1</sup> (1825)

Constitutional iodism—Rilhet<sup>2</sup> (1859)

Iodine exophthalmic goiter, iodine Graves' disease—Trousseau<sup>3</sup> (1860)

Formes frustes exophthalmic goiter—Trousseau<sup>4</sup> (1862), Marie<sup>5</sup> (1883)

Secondary Basedow—Gauthier<sup>6</sup> (1893), Buschan<sup>7</sup> (1894)

Basedowified goiter—Marie<sup>8</sup> (1897), Struma basedowificata—Kocher<sup>9</sup> (1906)

Goiter heart—Kraus<sup>10</sup> (1898)

Iodine thyroidism—Breuer<sup>11</sup> (1900)

Basedowid—Stern<sup>12</sup> (1908-1909)

Toxic nonexophthalmic goiter—Plummer<sup>13</sup> (1912)

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<sup>1</sup> Submitted for publication, Dec 28, 1928

<sup>\*</sup> From the Radium Clinic of Beth Israel Hospital, New York

1 Parry, C H. Collection from the Unpublished Medical Writings 2 111, 1825

2 Rilhet, F. Memoire sur l'iodisme constitutionnel, etc, presente a l'academie imperiale de medecine le II Janvier 1859, Gaz med de Paris, 1860, Avril

3 Trousseau, A. Du goitre exophthalmique, Gaz d hop 33 553, 1860

4 Trousseau, A. Du goitre exophthalmique ou maladie de Grave, Clinique, Paris 2 614, 1862

5 Marie, P. Contribution a l'etude et au diagnostic des formes frustes de la maladie de Basedow, These de Paris, 1882-1883, p 1

6 Gauthier, G (de Charolle). Des goitres exophthalmique, secondaires ou symptomatique, Lyon med 72 41, 82 and 120, 1893

7 Buschan, G. Die Basedow'sche Krankheit, eine Monographie Von der Berliner Hufel- und -Gesellschaft preisgekronte Arbeit, Leipsic und Vienna Franz Deuticke, 1894

8 Marie, P. Maladie de Basedow et goitre Basedowifie, Bull et mem Soc med d hôp de Paris 14 57, 1897

9 Kocher, T. The Pathology of the Thyroid Gland, Brit M J 1 1261, 1906

10 Kraus, F. Kropfherz Krankheiten der Schilddruse, in Ebstein und Schwalbe Handbuch der Praktischen Medizin, 1898 vol 2, p 240

11 Breuer, R. Aetiology der Basedow'schen Krankheit und des Thyreoidismus, Wien klin Wchnschr 13 641, 671, 1900

12 Stern, R. Differentialdiagnose und Verlauf des Morbus Basedowii und seiner unvollkommenen Formen, Jahrb f Psychiat u Neurol 29 179, 1908-1909

13 Plummer, H S, in discussion following paper by Marine, D. Anatomic and Physiologic Effects of Iodine on Thyroid Gland of Exophthalmic Goiter J A M A 59 325 (Aug 3) 1912

Toxic adenoma of the thyroid—Plummer<sup>14</sup> (1913)

Adenoma with hyperthyroidism—Plummer<sup>15</sup> (1916)

Hyperfunctioning adenomatous goiter—Plummer<sup>16</sup> (1921)

Iodine hyperthyroidism—Jackson<sup>17</sup> (1924)

Nodular goiter with hyperthyroidism—Rienhoff<sup>18</sup> (1927)

In a recent study of the goiter problem, Aschoff<sup>19</sup> stated "We were able to show that the nodular form was not a kind of hyperplasia or hyperplastic condition, as was then believed, but that we were dealing with a definite tumor formation, namely, adenomata." Do simple adenomas of the thyroid gland become toxic? "Indeed, they do," is Aschoff's affirmative reply. "Struma nodosa basedowificata," or toxic adenoma of the thyroid does exist. If simple nodular goiter is almost invariably synonymous with simple adenoma of the thyroid, toxic nodular goiter is equally synonymous with toxic adenoma of the thyroid. Hence, clinically, a tentative diagnosis of toxic adenoma of the thyroid is warranted whenever a nodular thyroid is associated with the constitutional symptoms of exophthalmic goiter with or without the ocular manifestations of the disease. This tentative clinical diagnosis is corroborated if iodine medication ameliorates<sup>20</sup> or aggravates<sup>21</sup> the symptoms, or if surgical enucleation or successful irradiation of the adenoma cures or markedly improves the patient.

#### REVIEW OF THE LITERATURE

Almost a century has elapsed since the names of Graves and Basedow have become closely associated with the clinical concept exophthalmic goiter. During this period of time, knowledge of this disease has grown and become vastly more extensive than that of its original discoverers. The so-called classic triad of symptoms—exoph-

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14 Plummer, H. S. The Clinical and Pathologic Relationship of Simple and Exophthalmic Goiter, *Am J M Sc* **146** 790, 1913

15 Plummer, H. S. The Function of the Thyroid Gland, Normal and Abnormal, *Tr A Am Phys* **31** 128, 1916

16 Plummer, H. S. Interrelationship of Function of the Thyroid Gland, *J A M A* **77** 243 (July 23) 1921

17 Jackson, A. S. Iodine as a Cause of Hyperthyroidism, *Lancet* **44** 324, 1924

18 Rienhoff, W. F., Jr. Hyperthyroidism and Its Relation to Benign Tumors of Thyroid Gland, *South M J* **20** 901 (Dec.) 1927

19 Aschoff, L. The Goiter Problem, Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924, pp 313-339

20 Graham, A., and Cutler, E. C. Exophthalmic Goiter and Toxic Adenoma. Similarity of Response to Iodine, *Ann Surg* **84** 497 (Oct.) 1926. Youmans, J. B., and Kampmeier, R. H. Iodine in Toxic Adenoma, *Arch Int Med* **41** 66 (Jan.) 1928

21 Kimball, O. P. Differential Diagnosis of Hyperthyroidism, *Ohio State M J* **20** 421 1924. Boothby, W. M. The Use of Iodine in Exophthalmic Goiter, *Endocrinology* **8** 727, 1924. Jackson, A. S. Goiter and Other Diseases of the Thyroid Gland, New York, Paul B. Hoeber, Inc., 1926

thalmos, tachycardia and goiter—is no longer considered absolutely essential for the correct diagnosis of the disease. *Formes frustes* have been described and recognized. The thyroid factor is no longer considered a mere secondary phenomenon among the essential manifestations of the disease. A definite, pathologic condition of the thyroid gland has gradually become more and more recognized as the essential underlying condition and mainspring of the disease.<sup>22</sup> Thyrotoxicosis, hyperthyroidism and dysthyroidism have become almost universally synonymous terms with exophthalmic goiter.

Nevertheless, greater knowledge and changed conceptions of the disease have not dimmed the memory nor marred the luster of the names of Graves and Basedow. With the passing of the years their fame and popularity, instead of being on the wane, appear to be on the increase. Moreover, not only in discussions of classic exophthalmic goiter are their names frequently on the lips of every tyro in medicine, but also in association with toxic adenoma of the thyroid. And yet neither Graves<sup>23</sup> nor Basedow<sup>24</sup> ever reported any cases that could have been classed with toxic adenoma. The first observer to whom this honor is due—as was recently pointed out by Sir Humphry Rolleston<sup>25</sup>—is no other than Caleb Hillier Parry who “in 1786, left an account of exophthalmic goiter so complete and original that it more justly entitles him to the honor of its discovery than either Flajani (1800), Graves (1835) or Basedow (1840).” In the same study, published posthumously in 1825, to which the distinguished American medical historian, Fielding

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22 Greenfield, W. E. The Bradshaw Lecture on Some Diseases of the Thyroid Gland, Delivered Before the Royal College of Physicians, *Brit M J* **2** 13 (Dec.) 1893. Joffroy, A., and Achard, C. Contribution a l'anatomie pathologique de l'maladie de Basedow, *Arch de med exper et d'anat path* **5** 807, 1893. Renaut. Corps thyroide et maladie de Basedow, *Semaine med* **15** 327, 1895. Farmer, E. Beitrage zur pathologische anatomie des Morbus basedowii mit besonderen Beruecksichtigung der Strumen, *Virchows Arch f path Anat* **143** 509, 1896. Muller, L. W. Beitrage zur Histologie der normalen und der erkrankten Schilddruse, *Beitr z path Anat u z allg Path* **19** 127, 1896. Hamig, G. Untersuchungen ueber Morbus basedowii, *Arch f klin Chir* **55** 1, 1897. Hansemann, D. Schilddruse und thymus bei der Basedow'schen Krankheit, *Berl klin Wchnschr* **42** 65 (Oct 30) 1905. Ewing, J. Exophthalmic Goiter from the Standpoint of Serum Therapy, *New York M J* **84** 1061 and 1114, 1906. Lewis, D. D. The Pathological Anatomy of Exophthalmic Goiter, *Surg Gynec Obst* **3**. 476, 1906. Kocher, T. The Pathology of the Thyroid Gland, *Brit M J* **1** 1261, 1906. Kocher, A. Die histologische und chemische Veranderung der Schilddruse bei Morbus basedowii und ihre Beziehung in Funktion der Druse, *Virchows Arch f path Anat* **208** 86, 1912.

23 Graves, R. J. *System of Clinical Medicine*, Dublin, 1835.

24 Basedow, K. *Exophthalmos durch Hypertrophie der Zellgewebe in der Augenhohle*, *Wchnschr f d ges Heilk*, Berlin, 1840, pp 199-204, 220-228.

25 Rolleston, Sir Humphry. Caleb Hillier Parry, M.D., F.R.S. *Ann M History* **7** 205, 1925.



H Garrison,<sup>26</sup> so eulogistically refers, there is also the first account of toxic adenoma of the thyroid reported in the medical literature

Miss P, of a gouty and nervous family, had had an enlargement of the thyroid for more than twenty years, which has been very much increased lately. The swelling began on the right side and is now nearly equal on the left but extending far upwards. It is not sore but occasionally uneasy. For the past eight or nine years, following an attack of gouty arthritis of several weeks' duration, she began to be subject to depression of spirits, frequent headaches, violent palpitation, extreme nervousness and moderate tachycardia. She has taken Bark, Sponge, Calomel, Antimony, Sarsaparilla, Soda, has tried sea bathing and used mercurial friction, which made her faint.

Although Parry was the original discoverer of exophthalmic goiter and toxic adenoma, he did not make any distinction between these two types of cases, for his view of the rôle of the thyroid gland in this disease—which eponymically should have been best known as Parry's disease—was far removed from the current theory of thyrotoxicosis. Instead of looking on the abnormal enlargement of the thyroid as a pathologic process responsible for the toxic clinical manifestations of the disease, he perceived in this enlargement a beneficent protective response. The physiologic function of the thyroid gland was entirely unknown during his time. Greatly impressed as he was by the enlargement of the thyroid gland, he was even more strikingly impressed by the headward throbbing carotids and the marked nervous and psychic manifestations of the disease. Hence, he concluded that the primary site and origin of the disease must be located in the brain, having been induced there by a morbid determination (flow) of blood—the current explanation for many nervous ailments during Parry's time.<sup>27</sup> But what puzzled Parry was that if this disease was a primary condition of the brain, what was the significance of the coincident enlargement of the thyroid gland? On further reflection and speculation, he came to the conclusion that "the coincidence is so frequent and remarkable that one can scarcely avoid suspecting that the thyroid gland, of which no use whatever has hitherto been hinted by physiologists is intended in part to serve as a diverticulum in order to avert from the brain a part of the blood, which, urged with too great force by various causes, might disorder or destroy the functions of that important organ."

If Parry assigned at least an important secondary—protective shunting—rôle to the thyroid gland in toxic adenoma, the next most important contributor to this interesting problem, Rilliet<sup>2</sup> of Geneva, almost entirely denied the significance of the thyroid in what has since most popularly become known as "iodine Basedow" or iodine hyperthyroidism. Under the title of "Constitutional Iodism," Rilliet,<sup>2</sup> in 1859, pub-

<sup>26</sup> Garrison, F. H. *History of Medicine*, Philadelphia, W. B. Saunders Company, 1914.

<sup>27</sup> Parry, C. H. *Elements of Pathology*, London, 1815, vol. 1, p. 187.

lished a comprehensive monograph in which he exposed the dangers of the administration of iodine both in the prophylactic and in the curative treatment for simple goiter. From a study of the literature and his own observations, he collected a series of cases in which after iodine medication there developed all the typical symptoms of toxic adenoma, namely, rapid loss in weight in spite of bulimia, diarrhea, tremor, tachycardia, mental disturbances, etc. Fairly illustrative of these observations is case 1 of his own series.

**RILLIET'S CASE**—A man, aged 50, had noticed since youth a hard, irregular tumor mass in the right lobe of the thyroid gland. The mass was symptomless, grew slowly and had reached the size of an orange in April, 1857, when the man accidentally first came under medical observation. Although the goiter was entirely symptomless, iodine medication was advised in order to induce the disappearance of the unsightly tumor mass. Within six days after iodine therapy was started, during which time the total dose of the drug taken barely exceeded 1 gram (0.065 Gm.) the patient developed rapid and progressive loss in weight. His eyes showed a definite stare. He became gloomy and depressed. His weakness became so profound that he was unable to attend to his occupation. There was a complete change in his personality. He became lachrymose and sleepless. His voice sounded cracked and tremulous. Both upper and lower extremities showed a definite tremor. With the progressive development of emaciation, the thyroid tumor shrank to three fourths of its former size, but the general condition of the patient had deteriorated greatly and his condition appeared to be so grave that a fatal issue was expected.

Under treatment with tonics and with a change of scene, the symptoms gradually subsided, but not before the lapse of seven months after the patient of his own accord had abruptly stopped taking the iodine and had wrathfully flung the medicine bottle with its unfinished contents into the lake of Geneva did he recover his former health.

With the complete regaining of his health and strength, the goiter returned to its original size and symptomless condition.

Of the twenty-three cases personally observed by Rilliet, twenty of the patients recovered, one had persistent symptoms at the time of the report, and two died. In addition, Rilliet found five deaths reported in the literature. In almost all these cases of so-called "constitutional iodism," with few exceptions, the toxic manifestations occurred in patients with clinically demonstrable preexisting goiter. In the majority of these cases, the goiter shrank during the height of the constitutional symptoms and returned to its former size when the patients recovered their former health. What interpretation was to be given to these important observations? What part did the goiter play in the origin and development of these toxic constitutional symptoms? Previous investigators Roser,<sup>28</sup> Prevost, Lebert<sup>29</sup> and others, who had made similar observations sug-

28 Roser. Ueber die sogenannte Jodkrankheit, richtiger Krankheit der vertriebenen Kropfe, *Arch f d ges Physiol* 7 74, 1848, Ueber Jodkrankheit und uber die kropfkachexie, falschlich auch Jodkrankheit genannt, *ibid* 3 494, 1859.

29 Lebert, H. Die Krankheiten der Schilddruse. Breslau, 1862, p 229.

gested resorption of abnormal goiter products as the underlying cause of the toxic constitutional symptoms. Rilliet considered this explanation untenable for three reasons:

1 Constitutional iodism has been observed among patients who clinically failed to show any goiter.

2 Constitutional iodism has been observed among patients in whom the thyroid swelling did not diminish at the height of the constitutional symptoms.

3 Constitutional iodism has not been observed in the great majority of patients whose goiters did disappear under treatment with iodine.

Nor did Rilliet agree with the view of the famous Parisian clinician, Trousseau, who suggested that "constitutional iodism" is merely atypical or latent exophthalmic goiter fanned into activity by iodine medication. Against this view he opposed the following differential diagnostic picture, the cardinal features of which hardly differ from those of recent publications on the differential diagnosis of toxic adenoma and exophthalmic goiter.

#### Constitutional Iodism

- 1 Fairly frequent in Geneva since the introduction of iodine therapy by Comdet<sup>o</sup> in 1820.
- 2 Onset after use of iodine in persons who previously were perfectly healthy.
- 3 Exophthalmos is absent.
- 4 Goiter is present for many months or years before the onset of the toxic constitutional symptoms.
- 5 Goiter is avascular, nonpulsatile.
- 6 Goiter decreases in size at the height of the toxic constitutional symptoms.
- 7 Goiter enlarges and returns to its former size when cachexia disappears.
- 8 Tremor is marked.
- 9 Bulimia is frequently present.
- 10 Loss in weight, in spite of bulimia, is always present.
- 11 Prognosis not very grave. The condition is only an incident in health. Remove the cause—iodine—and the patient usually gets well within a few months, without the return of the illness.

#### Exophthalmic Goiter

- 1 Not any more frequent in Geneva after than before the introduction of iodine therapy.
- 2 Onset without the use of iodine, although intake of iodine may have aggravated the symptoms.
- 3 Exophthalmos is present.
- 4 Toxic constitutional symptoms are present long before the appearance of goiter.
- 5 Goiter is vascular, pulsatile.
- 6 Goiter increases in size at the height of the toxic constitutional symptoms.
- 7 Goiter diminishes in size when cachexia disappears.
- 8 Tremor is faint or absent.
- 9 Bulimia is rarely present.
- 10 Loss in weight may be absent.
- 11 Prognosis grave. Cause unknown. Duration years. Relapses frequent. Mortality high.

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30 Toraude, L. G. Bernard Courtois (1777-1838) et la decouverte d l'iode (1811), Paris, Vigot Freres, 1921.

Being convinced in his own mind that "constitutional iodism" was a definite clinical entity in which neither simple nor exophthalmic goiter plays any significant part, Rilliet argumentatively queried, "Don't we admit the presence of an arsenical, lead, mercurial, or alcoholic cachexia? Why then deny to iodin a similar rôle?"

Rilliet's differential diagnostic picture failed to impress Trousseau. Prompt and incisive, Trousseau's<sup>3</sup> reply came back.

When we see that such feeble doses as 10 mgm of iodin given once in twenty-four hours are able to produce severe intoxications, when we are told by Rilliet that even a trip across the ocean in an iodin charged atmosphere is sufficient to bring in its trail all the symptoms of "Constitutional Iodism", we are inclined to think that these exposed individuals had already been affected with exophthalmic goiter. How else can one explain this contradiction between the experience of all other observers and those of Dr Rilliet unless we assume the prior existence of a morbid element which, under the stimulus of the iodine medication, has been aroused to markedly increased activity?

Every day, in every country, in Paris as well as in Geneva, iodin is given in large doses as high as two, three, or four grams in twenty-four hours. Never have any accidents occurred, although the same dose of the medication has been kept up for several weeks. Therefore, when we see, on the contrary, that almost infinitesimal doses of iodine do at times produce enlargement of the thyroid gland, bulimia, and various nervous manifestations, we must admit that in these exceptional instances we are dealing with cases of exophthalmic goiter.

In his reply, Trousseau<sup>4</sup> paid no attention to the presence or absence of exophthalmos as an important differential diagnostic point between "constitutional iodism" and exophthalmic goiter. For, in common with Parry and other observers, he had known of cases of exophthalmic goiter without exophthalmos. Indeed, so well informed was he on the variations of the clinical course of the disease that he discussed freely and deliberately forms frustes cases of exophthalmic goiter long before Pierre Marie, in 1883, wrote his famous thesis in which he called special attention to these atypical forms, in which at times neither clinically demonstrable goiter nor exophthalmos is present.

Although the subject of toxic adenoma had been thus unknowingly receiving considerable attention in the medical literature,<sup>51</sup> it did not loom large either as a theoretical or a practical problem until after the thyroid factor assumed the center of the stage in 1886, when Moebius<sup>52</sup> first formulated the thyrotoxic theory of exophthalmic goiter. When the inhibitions erected universally by the adherents of the neurogenic theory against incriminating the thyroid gland as the underlying cause of the toxic manifestations in exophthalmic goiter had been sprung by

51 Sattler, H. Die Basedow'sche Krankheit 2 537, 1910.

52 Moebius, P. J. Vom Verhältnisse der Polioencephalitis zur Basedow'schen Krankheit in Jendressik, E. Schmidt's Jahrbucher der Medizin 1886 vol 210, p 237.

Moebius' keen reasoning,<sup>33</sup> surgery at once boldly entered the therapeutic field. Thyroidectomy for the curative treatment of exophthalmic goiter suddenly received a tremendous impetus. Whereas until 1886, scarcely a dozen reports of surgical intervention in cases of exophthalmic goiter are contained among the 375 references quoted by Halstead<sup>34</sup> in his monograph on "The Operative Story of Goiter," within the next decade more than 100 reports are tabulated by Sattler<sup>35</sup> and Kinnicutt<sup>36</sup>.

It was soon perceived by every careful student of patients on whom thyroidectomy had been performed that the surgical results were strikingly different in cases of "primary" from those in "secondary" cases of exophthalmic goiter, in which the symptoms had supervened on an old preexisting goiter. Whereas in "primary" exophthalmic goiter the surgical failures were many and the recurrences frequent, the success after the initial mortality in cases of "secondary" or "goiter heart" was satisfactory. So strikingly different were these results that such eminent students of the disease as Gauthier,<sup>6</sup> Buschan,<sup>7</sup> Marie,<sup>8</sup> Kraus<sup>10</sup> and others who continued to cling to the nervous system as the primary site and origin of the disease, and assigned to the thyroid a mere secondary rôle in primary exophthalmic goiter, acceded to the thyroid a primary thyrotoxic rôle in secondary Basedow.

Briefly summarized, the chief arguments of these eminent clinicians in favor of the dual nature and origin of toxic goiter were as follows:

Exophthalmic Goiter	Secondary Exophthalmic Goiter, "Goiter Heart" (Toxic Adenoma)
1 Occurs in younger persons	1 Occurs in elderly persons
2 Goiter develops long after the onset of the toxic constitutional symptoms	2 Goiter exists for many years before the onset of the toxic symptoms
3 Exophthalmos is frequently present	3 Exophthalmos is frequently absent
4 The course of the disease is frequently severe	4 The course of the disease is often mild
5 Surgical intervention is rarely curative	5 Surgical intervention is frequently curative

The major objection, however, which was specially stressed by Kraus,<sup>10</sup> in 1898, against the unitary conception of exophthalmic goiter and "goiter heart" and against the thyrotoxic origin of primary exoph-

33 Moebius, P. J. Ueber des Wesen der Basedow'schen Krankheit, *Centralbl f Nerven u Psychiat* **10** 225, 1887.

34 Halstead, W. S. The Operative Story of Goiter, Reprint, *Bull Johns Hopkins Hosp* **19** 71, 1920.

35 Sattler, H. Die Basedowsche Krankheit, vol. 1, Leipzig, 1909.

36 Kinnicutt, F. P. The Theory of the Thyroid Origin of Graves' Disease with its Bearing on the Surgical Treatment of the Disease, *M Rec* **49** 541 (April) 1896.

thalmic goiter, was the failure, by means of thyroid products, to produce experimentally exophthalmos and the other ocular signs in the presence of all the other toxic phenomena of the disease

Hardly had this chief objection been formulated by Kraus when it was promptly answered by a series of fortuitous human clinical experiments reported by Notthaft,<sup>37</sup> Gauthier<sup>38</sup> and Bieuer.<sup>11</sup>

**NOTTHAFT'S CASE**—A man, aged 43, slightly distressed by obesity, was advised by a friendly druggist to try 5 gr (0.324 Gm) tablets of thyroid extract to produce a reduction cure. Within five weeks the patient consumed 1,000 such tablets. The result was a rapid loss of 30 pounds (13.6 Kg) in weight, accompanied by the development of all the symptoms of exophthalmic goiter, including exophthalmos. The medication was stopped at the beginning of the sixth week. Six months later the constitutional symptoms were diminished, but exophthalmos was still present. It was four months later before the patient fully recovered.

Even more illuminating was Gauthier's case.

**GAUTHIER'S CASE**—A woman, aged 50, had a slowly growing goiter of several years' duration. The tumor mass, more marked on the left, had reached the size of an orange. Presently, she began to suffer from dyspnea and orthopnea. She applied to a druggist who gave her an iodine preparation to be painted over the region of the neck and tumor. A few weeks later, failing to note any improvement, she again consulted the same druggist who prescribed, in addition, iodine medication internally. The result was the development a few days later of typical exophthalmic goiter with marked exophthalmos. She was treated medically, and four weeks later she began to show signs of improvement. Two or three months later, thyroidectomy was performed. Twenty-four hours after the operation, the patient died in a typical thyroid crisis. Necropsy failed to show any organic disease to account for this sudden death.

Equally illuminating and corroborative of these facts, showing the hidden relationship between "simple" and toxic goiter and the close relationship between toxic adenoma and exophthalmic goiter, were the observations of Bieuer in nine cases of goiter, of which the following three are excellent illustrations.

**BIEUER'S CASE 1**—A woman, aged 56, first came under observation on March 13, 1900, complaining of slight palpitation on exertion, slight headache and drawing pains in her legs.

Her past history was entirely negative except for a goiter which had first been noticed eighteen years prior to observation, during pregnancy. The goiter after growing rapidly in size for several weeks, had remained stationary ever since. The only two abnormal objective signs found on examination were a large soft goiter, a soft diastolic murmur over the sternum. The patient looked calm and

37 Notthaft, A. Ein Fall von artificiellen akuten thyreogenen Morbus basedowii, *Zentralbl. f. inn. Med.* **19** 353, 1898.

38 Gauthier, L. Encore l'iode et la glande thyroïde, *Rev. med. de la Suisse Rom.* **19** 618, 1899.

well nourished. She had no tremor, and her pulse was not accelerated. A diagnosis of arteriosclerosis was made, and iodine medication was prescribed. For two weeks, with an interruption of nine days between, she took a daily dose of 0.9 Gm. Within less than a week after the medication was started the patient developed rapid reduction in the size of the goiter, marked restlessness, tremor, flashes of heat, rapid loss in weight in spite of good appetite and twenty diarrheal stools daily. The frequency of the pulse rate rose to 120. The thyroid gland was found to have shrunk considerably in size, and on palpation, a node, the size of a hazel-nut, was felt in the left lobe of the gland. Exophthalmos and von Graefe's sign were absent, but a slight stare and Stellwag's sign were detected. The symptoms continued for several weeks after the medication was discontinued, and when the patient was last examined her pulse rate was still 100.

CASE 3—A woman, aged 58, had an old goiter which had never caused any Basedow symptoms. Within one week after taking 10 Gm of potassium iodide for arthritic pains, she developed headaches and marked weakness. She stopped the medication, but the weakness kept increasing. The goiter had shrunk only slightly, but the patient became irritable and developed marked tremor and tachycardia. There was rapid wasting, especially of the breasts. Diarrheal stools were frequent but painless. On examination, exophthalmos was absent but all the other ocular signs of exophthalmic goiter were present, namely, stare and Dalrymple, Stellwag and von Graefe's signs. Her pulse rate was 100. Slow improvement was first noticed one month after the iodine medication was discontinued.

CASE 6—A woman, aged 30, had a "thick neck" since youth. She had always been well, had never been nervous or shown symptoms of exophthalmic goiter. Her weight before the onset of her present illness was 130 pounds (59 Kg.). Purely for cosmetic reasons, she wished to reduce the size of her thick neck, which measured 38 cm in circumference. At the advice of a physician she took thyroidin tablets for four weeks, but failed to notice any reduction. She was then given an ointment of iodine-potassium-iodide to rub into the neck daily. This treatment was carried out for a period of forty-four days. The goiter began to shrink in size, but simultaneously with this shrinkage the patient began to lose weight rapidly. She grew nervous and developed palpitation even at rest. She stopped the medication, but her symptoms persisted. Her skin felt hot. She grew weak, and was annoyed by polyuria. She perspired excessively and suffered from bulimia. Twenty days after the iodine medication was discontinued, examination showed a parenchymatous goiter with two small nodular masses in the left lobe of the gland. In addition to tremor and tachycardia, definite bilateral exophthalmos and positive Stellwag and von Graefe's signs were present.

From a study of these three cases and similar ones, Bieuer came to the conclusion that all the toxic phenomena in "iodin-thyroidism" as well as in typical exophthalmic goiter are due to resorption of thyroid products. He explained the absence of eye phenomena in some cases and their presence in others on the basis of special local vasomotor and ocular resistance or susceptibility, just as Kraus has assumed that in "goiter heart" there is a special cardiovascular vulnerability to the action of the resorbed thyroid products. Viewed by the light of these observations, Bieuer felt that the unitary conception of exophthalmic goiter was thus indicated and Kraus' objections fully answered.

This unitary conception of toxic goiter originally formulated by Moebius<sup>39</sup> had been repeatedly stressed by its author in numerous publications. As late as 1906, after a score of years of intensive study and investigation of this important problem, Moebius<sup>39</sup> failed to perceive any fundamental distinction between the various types of toxic goiter. He maintained:

The symptoms in secondary Basedow present the same characteristics as in the primary form. The cardiac disturbances, exophthalmos, and mental changes occur equally in both. It matters little whether the goiter preceded the symptoms by one year or fifteen years. It is incorrect to speak of complete and incomplete Basedow. We should rather classify our cases into mild and severe forms, into those presenting many or few symptoms.

These views so tersely and emphatically expressed by Moebius kept gaining ever wider recognition among clinicians and pathologists toward the end of the first decade of the twentieth century. As late as June 1909, L. B. Wilson,<sup>40</sup> the director of the pathologic department of the Mayo Clinic, emphatically declared:

In examining cases of so-called simple goiter for exophthalmic symptoms we must get completely away from our old teachings that exophthalmos is a *sine qua non* of Graves' disease. The disturbed nervous, metabolic and muscular phenomena are quite essentially diagnostic. Looked at from the clinical standpoint then, a case of Graves' disease is one with an enlarged thyroid and exhibiting symptoms of too much thyroid secretion, while a case of simple goiter is one with an enlarged thyroid, but exhibiting no such symptoms.

Even more emphatic at this time in his unitary attitude toward toxic goiter was Charles H. Mayo.<sup>41</sup> In discussing the operative treatment of "hyperthyroidism," he stated:

The name commonly used exophthalmic goiter, is not a good term as many of the patients do not have a goiter and others do not have a prominent eye, while some of them have neither of these symptoms in the early stages of the disease when a diagnosis might be made if these symptoms were not considered of so much importance. In a death from an unoperated acute Graves' disease in which the thyroid was apparently normal to palpation both before and after death, the autopsy showed the gland to weigh nearly three times the normal, and to be typical in the structural changes present.

However, while this unitary conception of toxic or exophthalmic goiter was being publicly championed in print by Wilson and Mayo, an undercurrent of doubt was gradually emerging and sweeping aside the

39 Moebius, P. J. *Die Basedowsche Krankheit*, Wien 1906.

40 Wilson, L. B. *The Pathological Relationship of Exophthalmic Goiter and Simple Goiter*, *Surg. Gynec. Obst.* 8: 588, 1909.

41 Mayo, C. H. *The Operative Treatment of Hyperthyroidism*, *Surg. Gynec. Obst.* 8: 602, 1909.



former unified point of view among the members of the Rochester Clinic. The first to recede from his former unitary view was the pathologist, Wilson.<sup>42</sup> Only four years later, in 1913, he declared

The solution of problems of the pathology of the thyroid has long been rendered more difficult by indefinite clinical diagnoses and nomenclature. While non-toxic cases usually have been diagnosticated, "Simple goiter," yet many cases with mild symptoms have also been called "simple goiter," and many cases, though not true exophthalmic yet markedly toxic, have been called by most clinicians "exophthalmic goiter."

Though a sharp distinction between the two clinical types of toxic cases—exophthalmic and non-exophthalmic—had not been made in 1908, I was able to show that pathologically there were two distinct types of glands to be found among thyroids removed from toxic goiter cases.

Hypertrophies, hyperplasias, and extreme regenerations, constituted 79 per cent of the total number of specimens examined, while fetal and colloid adenomas, the adenomatoses and the so-called simple thyroids, constituted 21 per cent of the specimens examined.

In reviewing the clinical data of his more recent cases, Plummer has found that practically all, if not all, of the cases of true exophthalmic goiter lie in the pathological groups showing hypertrophy and hyperplasia, while the toxic non-exophthalmic cases are scattered among the other pathological groups.

Even more emphatic of the dual character of toxic goiter is Plummer's<sup>18</sup> own original contribution which appeared simultaneously with Wilson's. He declared

Exophthalmic goiter is a definite clinical complex always associated with hyperplasia of the thyroid, and should be sharply distinguished from the constitutional state or states that may develop with non-hyperplastic goiter.

Can we associate the symptom-complex of non-hyperplastic toxic goiter with any definite pathological change in the thyroid? For the present this question must be answered in the negative.

This negative answer, however, is not entirely consistent with an important positive statement made incidentally in the text. Although the close identification of toxic nonhyperplastic goiter with toxic or "hyperfunctioning" thyroid adenoma had not as yet been definitely formulated in Plummer's mind, nevertheless the budding growth of this hypothesis can be perceived clearly emerging through the lines. In referring to the thyrogenic origin of exophthalmic goiter, he stated

While I do not wish to enter into a discussion of this subject at the present time, I wish to call attention to a point in support of this theory that, as far as I know, has not hitherto been made, namely that an individual, 22 years, with an adenoma of the thyroid has a definite chance of developing a train of symptoms during the thirty-sixth year so similar to the symptom-complex associated with hyperplastic thyroid that the best-trained diagnosticians are constantly confusing the two conditions.

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<sup>42</sup> Wilson, L. B. The Pathology of the Thyroid Gland in Exophthalmic Goiter, *Am J M Sc* **146** 781, 1913.

Precisely how definite this chance is when judged by the frequency of association of adenomas with toxic nonexophthalmic goiter at the time of operation at the Mayo Clinic was discussed by Wilson the following year in two contributions<sup>43</sup> In a study of the pathology of 374 thyroids from toxic nonexophthalmic goiter,<sup>44</sup> the following distribution of the adenomas was found

1 In 155 cases, "clinically in Plummer's sub-group I, i e., cases in which the clinical picture closely resembles and, in many instances, cannot be differentiated from, the cardiovascular complex resulting from alcoholic, syphilitic, septic, and other well-known toxins," early fetal adenomas constituted 7 per cent, degenerating fetal adenomas, 14 per cent, adult "colloid" adenomas, 21 per cent, secondary regeneration of atrophic parenchyma of "colloid" goiter, 17 per cent, atrophic parenchyma, "colloid" thyroids, adenomatoses, etc., 2 per cent

2 In 129 "cases with symptoms closely approaching the picture of Graves' disease," early fetal adenomas constituted 12 per cent, degenerating fetal adenomas, 33 per cent, adult "colloid" adenomas, 3 per cent, secondary regeneration of atrophic parenchyma of "colloid" goiter, 50 per cent, atrophic parenchyma, "colloid" thyroids adenomatoses, etc., 2 per cent

3 In ninety cases with mild or doubtful toxic symptoms of exophthalmic goiter, early fetal adenomas represented 10 per cent, degenerating fetal adenomas, 18 per cent, adult "colloid" adenomas, 19 per cent, secondary regeneration of atrophic parenchyma of "colloid" goiter, 9 per cent, atrophic parenchyma, "colloid" thyroids, "adenomatoses," etc., 44 per cent

An association of from 42 to 44 per cent of adenomas with toxic nonexophthalmic goiter is sufficiently interesting and instructive to invite investigation into its significance But of what proof is this association per se that the adenomas stand in any etiologic relationship to the development of thyrotoxic symptoms? Did not Wilson's further studies<sup>45</sup> record the fact that in a series of 2,356 thyroids from patients on the "simple goiter" list 45 per cent—the same proportion as in the toxic group—were composed principally of encapsulated adenomas, while the 17 per cent of patients on this list who presented toxic symptoms had thyroids showing histologically "secondary regenerations" and no adenomas? Were there any specific microscopic changes in the adenomas

43 Wilson, L B A Study of the Pathology of the Thyroids from Cases of Toxic Nonexophthalmic Goiter, *Am J M Sc* **147** 344, 1914, Relation of the Pathology and the Clinical Symptoms of Simple and Exophthalmic Goiter, *J A M A* **62** 111 (Jan 10) 1914

44 Wilson (footnote 43, first reference)

45 Wilson (footnote 43, second reference)

of the clinically toxic group which were not present in the adenomas of the atoxic group? If, as stated by Wilson, the same microscopic changes were found in both groups of cases, what were the reasons that prompted Plummer to embrace the assumption of toxic adenoma or hyperfunctioning thyroid adenoma?

Apparently the chief, if not the only, reason at this time that induced Plummer to embrace the hypothesis of toxic adenoma was the important clinical observation that in "adenoma with hyperthyroidism" the toxic phenomena disappear within a few weeks after the enucleation of the adenoma—in other words, the same clinical observations which long ago had made Gauthier,<sup>6</sup> Buschan,<sup>7</sup> Marie,<sup>8</sup> Kiaus<sup>10</sup> and others formulate their dual theory of toxic goiter.

The stimulus derived from this clinical observation alone, the constancy of which, according to Plummer, remains unchanged at the Mayo Clinic until recent date, would have sufficed to render strong support to the clinical assumption of toxic nodular goiter or toxic adenoma of the thyroid. Suddenly and unexpectedly, laboratory research set free an agent that was destined to exert a powerful stimulus to convert this assumption of toxic adenoma or hyperfunctioning thyroid adenoma into a firm, well grounded scientific hypothesis. This released agent, the most active constituent of the thyroid gland, was the newly discovered chemical decomposition product—thyroxin.<sup>46</sup>

In 1914, Kendall separated from the thyroid gland by means of alkaline alcoholic hydrolysis two groups of iodine compound—group A, insoluble in acids, and group B, acid soluble. By further hydrolysis of the A group, the compound containing iodine was separated in pure crystalline form, while no definite substance was isolated from the B group. Although the total iodine of the gland was found equally divided between the two groups, their physiologic and pharmacologic activity was strikingly unequal and dissimilar.

In testing B for physiologic activity, it was found that no apparent effects are produced when B is given experimentally to a normal animal or human being, but that a considerable degree of activity is manifest when B is given to patients suffering from cretinism, myxoedema and certain conditions of the skin.

No toxic effects have been produced by the administration of B even in large amounts.

In strong contrast to this nontoxic effect of B is the action of A.

It was found that the typical effects of administration of desiccated thyroid—rapid increase in pulse rate and vigor, increase in metabolism with loss in weight, and increase of nervous irritability—are all produced by the A constituents.

through all the various stages of purity, up to and including the crystalline compound containing 60 per cent of iodine. Although both

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<sup>46</sup> Kendall, E. C. The Isolation in Crystalline Form of the Compound Containing Iodine, Which Occurs in the Thyroid. Its Clinical Nature and Physiologic Activity, *J. A. M. A.* **64** 2042 (June 19) 1915, *Experimental Hyperthyroidism*, *ibid.* **69** 612 (Aug. 25) 1917.

A and B contain iodine the toxicity of A is in direct proportion to its iodine content, but B iodine given in equal amount produces no apparent effect.

The actual amount of the crystalline iodine compound necessary to produce marked effect is exceedingly small. A total of 11 mg (one-sixth grain), given in divided doses during a period of fourteen days to a cretin weighing forty pounds, increased the pulse rate from 90 to 140. A total of 30 mg (one-half grain), given in divided doses over a period of eighteen days to a woman weighing 112 pounds, increased the pulse rate from 75 to 130.

Further observations by Plummer<sup>46</sup> showed that in a normal person "2 mg of thyroxine a day may hold the basal metabolism 20 to 30 per cent above normal, 3 mg a day may hold the basal metabolism 50 per cent above normal."

These chemical and physiologic discoveries led Plummer to formulate the following deductions:

1 Hyperthyroidism is the physiologic state of an individual otherwise normal when the thyroxine in the tissues is sufficient to hold the basal metabolism above normal.

2 Hypothyroidism is the opposite of hyperthyroidism.

3 All the phenomena of pure hyperthyroidism are those that must attend a sustained elevation of the basal metabolism.

4 The status of hyperfunctioning adenomatous goiter is the result of a pure hyperthyroidism. The assumption that the status of adenomatous goiter is attributable simply to an excess of the normal thyroid product (pure hyperthyroidism) rests largely on a correlation of at least approximately accurate observations.

They are

The physiologic status of a thyroidless individual returns to normal when the basal metabolism is brought to normal by the administration of thyroxine.

The phenomena induced by the administration of thyroxine and the phenomena associated with adenomatous goiter are identical and are those that must attend a sustained elevation of the basal metabolism.

These phenomena disappear with the dropping of the basal metabolism to normal within three weeks after the enucleation of the adenoma.

The status of exophthalmic goiter, while in the main hyperthyroid, cannot be attributed wholly to an excess of the normal thyroid product. The characteristics of exophthalmic goiter may be due to an incomplete thyroxine molecule.

If, in addition to these differential features, is added Plummer's further statement<sup>47</sup> that iodine is either ineffectual or harmful in the management of toxic adenoma and is of marked temporary benefit in the treatment for exophthalmic goiter, then all the basic reasons on which the concept of toxic adenoma of the thyroid was built up have been enumerated.

<sup>47</sup> Plummer, H. S. *The Thyroid Gland*. St. Louis, C. V. Mosby Company, 1926.

How was this concept of toxic adenoma of the thyroid received in the scientific medical world?

The answer to this question can best be found from a consideration of the response of the pathologists, the surgeons, the internists, roentgen therapists and the radium therapists

*The Response of the Pathologists*—With the single exception of the pathologists<sup>48</sup> of the Mayo Clinic, where this hypothesis originated, few pathologists of note on the American continent embraced this clinical-pathologic concept of toxic adenoma. In the latest editions of such standard textbooks on pathology as those of MacCallum<sup>49</sup> and Delafield, Prudden and Wood<sup>50</sup> not a single word is mentioned about toxic adenoma. "I have observed Graves' symptoms with a fetal adenoma of the thyroid during a period in which the thyroid tumor was invaded by mammary carcinoma," is all Ewing<sup>51</sup> had to say about toxic adenoma of the thyroid. Karsner,<sup>52</sup> who devoted a few paragraphs to this problem, stated that the proofs submitted thus far are inadequate to establish the authenticity of toxic adenoma as a clinical-pathologic entity. Stengel and Fox<sup>53</sup> were noncommittal on the subject. They shifted both the concept and the burden of proof on the shoulders of the clinician. In discussing the pathologic anatomy of the thyroid gland in exophthalmic goiter and toxic adenoma, they declared

Adenomatoid goiter of papillomatous type is usually believed by clinicians to be present in exophthalmic goiter. These forms are general, but in certain instances the hyperplasia tends to remain in isolated areas or nodules. Such cases may give toxic symptoms and are designated "toxic adenomata" by clinicians. Such areas are usually multiple.

In contrast to the negative or noncommittal attitude of the great majority of American pathologists is the ready acceptance of this hypothesis by a number of their eminent European colleagues<sup>54</sup>. In a recent discussion of the goiter problem, Aschoff stated

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48 Wilson, L. B. The Pathology of Nodular (Adenomatous?) Goiters in Patients With and Those Without Symptoms of Hyperthyroidism, *Am J M Sc* **165** 738, 1923

49 MacCallum, W. G. Text Book of Pathology, Philadelphia, W. B. Saunders Company, 1925

50 Delafield, F., and Prudden, T. M. Text-book of Pathology, revised by Wood, 1927

51 Ewing, J. Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922, p. 898

52 Karsner, H. T. Human Pathology, Philadelphia, J. B. Lippincott Company, 1926, p. 843

53 Stengel, A., and Fox, H. A Text-Book of Pathology, Philadelphia, W. B. Saunders Company, 1927

54 Aschoff (footnote 19) Muir, R. Textbook of Pathology, Philadelphia, J. B. Lippincott Company, 1924. Wegelin, C., in Hende, E., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1927, vol. 1, p. 228

We were able to show that the nodular form was not a kind of hyperplasia but a definite tumor formation, namely adenomata. I lay great stress upon the distinction between simple hyperplasia and tumor formation. With a real tumor formation there may be hyperfunction, or dysfunction, or hypofunction. With you [Americans] only the Basedow gland and the toxic adenoma, which correspond with our nodular proliferating and parenchymatous colloid goiters, are concerned in hyperthyroidism. We deliberately also include the diffuse colloid goiter, but only the proliferating form of it.

Running in a similar vein are the views of Carl Wegelin, the successor of Langhans at the university of Bern, the most famous city in Switzerland for the study of goiter pathology during the past two hundred years.

*The Response of the Surgeons*—Numerous, although not entirely unanimous, are the members of the surgical specialty who embraced Plummer's hypothesis of the dual nature of thyrotoxicosis.<sup>55</sup> While the overwhelming majority of surgeons throughout the world unequivocally subscribed to Plummer's views on toxic adenoma as a clinical entity distinct from exophthalmic goiter, a number of prominent surgeons who perform operations on the thyroid are definitely opposed to this dual concept.

Crotti<sup>56</sup> stated

So far as exophthalmos is concerned, any one, I am sure, has observed severe cases of primary thyrotoxic goiter or the "exophthalmic goiter" of Plummer without any ocular symptoms whatever. On the other hand, in secondary thyrotoxic goiter, or "adenoma with hyperthyroidism" of Plummer, more than once the ocular symptoms have been very marked, exophthalmos included. So far as the other symptoms are concerned, although again usually not so intense or so frequent as in the primary form of thyrotoxicosis, they are so frequently enough present to preclude a fundamental clinical distinction.

The surgical results obtained speak also against any fundamental clinical difference of these two conditions.

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55 Mayo, C. H. Adenoma with Hyperthyroidism, *Ann Surg* **72** 134 (Aug) 1920. Frazer, C. H. The Management of Toxic Goiter from the Surgical Point of View, *Ann Surg* **72** 155 (Aug) 1920. De Courcy, J. L. Results Following Two Hundred and Forty-Five Thyroidectomies, *Am J Surg* **35** 342 (Nov) 1921. Haggard, W. D., and Dunkley, F. D. Thyrotoxic Adenoma, with Remarks on Basal Metabolism in Diagnosis of Goiter, *Surg Gynec Obst* **35** 553, 1922. Jackson, A. S. Iodine Hyperthyroidism, *Am J M Sc* **170** 271, 1925. Chapman, T. L. Lowering of Mortality in Treatment of Toxic Adenoma of the Thyroid, *Minnesota Med* **8** 653, 1925. Hoalst, J. Weitere Beitrage zur Pathologie und Therapie der toxischen Stumen, *Acta chir Scandnav* **61** 385, 1927. Abell, I. Multiple Adenomata of the Thyroid, *S Clin N Amer* **2** 1325, 1922.

56 Crotti, A. Thyroid and Thymus, Philadelphia, Lea & Febiger, 1922.  
p 351

Hertzler<sup>57</sup> declared

It is a mistake to do a mere enucleation in toxic adenoma the whole gland of toxic adenoma is diseased The histology indicates that it is injured beyond repair According to present methods we remove a part of the diseased tissue This is unsurgical The demands of ideal surgery dictate that the whole of the diseased tissue shall be removed The question is, are we able at this time to meet the ideals in the surgical treatment? The result is myxoedema This myxoedema can be controlled by the use of thyroid extract There are no more comfortable persons than these myxoedemics who take their grain a day

Whether any one will accept Hertzler's impressions as a correct characterization of "these myxoedemics" or doubt the value of the price paid, his failure to relieve the symptoms in toxic adenoma by mere enucleation is sufficiently illuminating to deserve emphasis

Speaking from a vast experience, second only to that of the Mayo Clinic, the astute clinician and brilliant surgeon<sup>58</sup> of the famous Cleveland Clinic declared "Clinical evidence of the functional activity of adenomata is found in the frequent development of symptoms identical with those which are characteristic of exophthalmic goiter and in the disappearance of those symptoms after the removal of the adenoma" Having made this admission of the existence of a clinical group of cases of toxic goiter to which the term toxic adenoma is applicable, Crile does not fail to make it clear that he does not perceive a fundamental distinction between toxic adenoma and exophthalmic goiter The former he considers only a phase or a stage in the development of the latter Hence, he continued, "it would seem as if adenoma caused every grade of toxemia, progressing from myocarditis, increased blood pressure, nervousness, and increased basal metabolism to true exophthalmic goiter" In discussing operative technic, he disclosed the fact that the surgical problem in toxic adenoma of the thyroid is not always that of a simple and safe enucleation "In extremely grave cases it may be necessary to diminish the thyroid activity by multiple steps, ligation of one vessel, ligation of the second vessel, partial lobectomy, complete lobectomy, when necessary allowing intervals of a month or more between any two of these stages"

One of the most recent and formidable combatants against the dual theory of thyrotoxicosis and against toxic adenoma, either as a clinical or as a pathologic entity, is Rienhoff<sup>59</sup> of Johns Hopkins Hospital From a study of 1,019 cases of toxic goiter at that institution during the past

57 Hertzler, A E The Development and Nature of the So-Called Toxic Adenomas, *Endocrinology* **10** 175, 1926

58 Crile, G W Toxic Adenoma in Relation to Exophthalmic Goiter, *Ann Surg* **72** 141, 1920

59 Reinhoff, W F, Jr Hyperthyroidism and its Relation to Benign Tumors of Thyroid Gland, *South M J* **20** 901, 1927

quarter of a century, Rienhoff came to the conclusion that pathologically, thyroid hypertrophy and hyperplasia is the underlying cause of the disturbance in both cases of exophthalmic goiter and cases of nodular goiter with hyperthyroidism (toxic adenoma). Neither in their clinical course, response to iodine, or surgical results, did toxic adenoma at Johns Hopkins differ from classic exophthalmic goiter except as the variation of a single disease, which in different persons may run different grades of severity. Rienhoff's objections to the dualistic theory of toxic goiter are deeper and more fundamental than those of the other dissenting surgeons. He maintains—and is sustained by one of the oldest students of the pathology of exophthalmic goiter in America, Dean Lewis<sup>60</sup>—that the pathologic histology in toxic adenoma does not differ in its essential characteristics from that of exophthalmic goiter. The only difference is that of extent and of degree of involvement of the gland. Whereas in the typical severe cases of exophthalmic goiter at the height of the clinically toxic stage of the disease, microscopic studies usually reveal diffuse hypertrophy and hyperplasia, in the milder forms of exophthalmic goiter or in toxic adenoma a localized or patchy hypertrophy and hyperplasia is found. Clinically, these patchy areas of hypertrophy and hyperplasia are felt as nodules in the thyroid, and are most frequently the cause of toxic nodular goiter. It is these localized patches of hypertrophy and hyperplasia, frequently surrounded by areas of fibrosis, which have been erroneously interpreted by pathologists as true neoplastic formations, namely, adenomas. True neoplasms, true adenomas, Rienhoff contended, do occur but have been found in only 8 per cent of the cases of nodular goiter with hyperthyroidism at the Johns Hopkins Hospital.

Moreover, with his studies and observations as a basis, Rienhoff expressed the belief that in toxic nodular goiter a state of diffuse hypertrophy and hyperplasia precedes the development of the nodular areas. These localized nodular enlargements occur when due to either iodine medication or spontaneous regression, discrete areas of the affected gland fail to involute or undergo hyperinvolution. When an exacerbation of the disease occurs, the morbid process may manifest itself either in the localized areas or in the nodules, leaving the surrounding parenchyma unaffected, or, which is more frequently the case, the nodular masses become the seat of pathologic activity while the intervening tissues remain normal. In either case one is not dealing with a single toxic nodular area or toxic adenoma but most frequently with multiple toxic adenomas or diffuse hyperplasia of the entire gland. Hence as far as the surgical therapeutic indications are concerned Rienhoff came to

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60 Rienhoff, W. J., Jr., and Lewis, D. D. Relation of Hyperthyroidism to Benign Tumors of the Thyroid Gland, *Arch Surg* **16**: 79 (Jan.) 1928.



the same conclusion as Crotti, Hertzler and Crile that the best results are obtained by a subtotal thyroidectomy and not by a mere enucleation

Are these observations that toxic adenoma usually spells toxic adenomas merely confined to the experience of the previously mentioned surgeons? Are only Goetsch,<sup>61</sup> Lahey,<sup>62</sup> Else,<sup>63</sup> Terry<sup>64</sup> and others the only ones who find that in toxic adenoma as in exophthalmic goiter successful surgical intervention necessitates subtotal thyroidectomy? Does the experience of the surgeons at the Mayo Clinic who perform operations on the thyroid completely corroborate Plummer's contention that a mere enucleation of the adenoma cures the patient of his toxic symptoms in three weeks? Let one consult Judd<sup>65</sup> from the Mayo Clinic, whose surgical late-results in toxic adenoma are open for inspection

In a series of 100 cases of toxic adenoma of the thyroid in which operation had been performed Judd reported the presence of the adenomas as follows: right and left lobes involved, forty-nine cases, right lobe, isthmus and left lobe, fourteen cases, right lobe and isthmus, four cases. In only 33 per cent of the cases was the adenomatous process on gross clinical examination limited to the isthmus or one lobe. Did Judd obtain the best results with a mere enucleation? Does he recommend enucleation as the method of choice in operating for toxic adenoma? Apparently not, for he stated that "in most cases the best operative results are obtained by subtotal thyroidectomy, which is accomplished by removing all except the posterior part of each lobe. The immediate benefit derived from the operation is greater than if lobectomy is done." Did all the patients with toxic adenoma of the thyroid who were operated on by such an eminently experienced surgeon like Judd recover in three weeks, as claimed by Plummer repeatedly in his various publications? Decidedly not. A careful review of the results at the end of two years postoperatively shows that nine patients died from all causes, two were not benefited, six showed the presence of tremor, eleven, change of voice, seventeen, loss of strength, twenty-three, tachycardia, twenty-eight, dyspnea, twenty-nine, palpitation, and forty-five, nervousness

61 Goetsch, E. The Pathology, Diagnosis and Surgical Treatment of Goiter, *Northwest Med* **21** 97, 1922

62 Lahey, F. H. The Treatment of Adenomata of the Thyroid, *S. Clin. N. Amer.* **4** 1395, 1924

63 Else, J. E. Adenomatosis or Diffuse Adenomatous Goiter, *J. A. M. A.* **85** 1878 (Dec 12) 1925

64 Terry, W. E. Surgical Considerations of Goiter, *Northwest Med* **21** 324, 1922

65 Judd, E. S. Results of Operation for Adenoma with Hyperthyroidism and Exophthalmic Goiter, *Ann. Surg.* **72** 145 (Aug.) 1920

If the observations of these eminent surgeons are correct, what remains then of the dual structure erected by Plummer to distinguish toxic adenoma from exophthalmic goiter? Is it the difference in response to iodine? But have not Kious,<sup>10</sup> Giam,<sup>20</sup> Rienhoff<sup>21</sup> and others shown that this difference in response does not always hold true? Has it not been shown that every form of hyperplastic goiter, whether diffuse as in exophthalmic goiter or patchy and discrete as in toxic adenoma, will for a time respond to medication with iodine and be followed by marked improvement in clinical symptoms? Is it only the inability to produce exophthalmos experimentally by administration of thyroxin which finally distinguishes toxic adenoma from exophthalmic goiter? But has not even this final objection been overcome by numerous observations in the past and by the recent experimental results of Kunde,<sup>66</sup> who by means of thyroxin did succeed in producing the complete clinical picture of exophthalmic goiter, including exophthalmos?

If, as a whole, Plummer's hypothesis of toxic adenoma as fundamentally different from exophthalmic goiter is untenable, what clinical lessons of importance can be learned from a close study of the immense number of contributions on this most important problem? Briefly summarized, these lessons are

- 1 Toxic adenoma and exophthalmic goiter are merely variations of a single disease. Eponymically, Parry's disease is the most appropriate designation, for Parry is the first observer who described all varieties of toxic goiter.

- 2 Clinically, a nodular goiter without exophthalmos may be as toxic or even more toxic than one with ocular manifestations. The prognosis in a severe case of toxic adenoma with myocardial insufficiency is much graver than in a moderately severe case of exophthalmic goiter with markedly bulging eyes, but with the myocardium fairly intact.

- 3 Although toxic adenoma may run as severe a course as exophthalmic goiter, its course is usually milder, and the surgical results are usually more satisfactory than in classic exophthalmic goiter.

- 4 The more favorable results in toxic adenoma are not due to any fundamental difference in nature from exophthalmic goiter but to a variation of a single disease. In exophthalmic goiter, the entire gland is diffusely involved in the pathologic process, hence, the symptoms are usually more marked and surgical resection is less satisfactory. In toxic adenoma, the thyroid gland shows one or several areas of involvement with intervening healthy tissue between the affected areas, hence the symptoms are usually milder and surgical resection more satisfactory. However, it is only in about one third of the cases of toxic

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66 Kunde, M. M. Studies on Metabolism. Experimental Hyperthyroidism. *Am J Physiol* **82** 195, 1927.

adenoma at the Mayo Clinic that the lesion has been found single. In the majority of cases, the adenomas are scattered throughout the gland. Moreover, in a number of instances, the adenomas are in state of regression, while the intervening parenchyma may be the seat of the disease. Hence the practical deduction of almost all surgeons who perform operations on the thyroid glands has been that subtotal thyroidectomy as the method of choice is the treatment not only for exophthalmic goiter but also for toxic adenoma.

*The Response of the Internists*—In contrast to the relatively large number of eminent surgeons whose vast personal experience with toxic adenoma had made them assail as untenable Plummer's theoretical and practical deductions about the dual nature of toxic goiter, is the small number of prominent internists who have joined the ranks of the dissenters. Plummer's dictum that toxic adenoma—adenoma with hyperthyroidism—is to be distinguished sharply from exophthalmic goiter both as a clinical and as a pathologic entity, and is to be considered essentially a surgical disease, found its staunchest adherents not only among the surgeons but also in the ranks of the internists. A review of medical publications, textbooks and systems of medicine shows almost a unanimous and unqualified acceptance of Plummer's teachings. Even internists who are in favor of submitting patients with severe cases of classic exophthalmic goiter to a course of medical treatment before referring them for operation are in favor of surgical intervention in toxic adenoma as soon as a positive diagnosis is made. Such an ardent advocate of the nonsurgical treatment for exophthalmic goiter as Bram,<sup>67</sup> who declared that he does not accept as rational any operative procedures on the thyroid in exophthalmic goiter except as an emergency measure when marked pressure phenomena threaten the life or comfort of the patient, is prompt to emphasize that toxic adenoma is from the start essentially a surgical disease.

What is the explanation for this apparently anomalous attitude of almost all internists toward toxic adenoma?

The explanations are many, but the chief reasons are threefold.

**Clinical** The observation is that local attack on the thyroid by surgical measures does yield strikingly better results in toxic adenoma than by any medical measures undertaken either for this thyrotoxic condition or for typical exophthalmic goiter.

**Pathologic** The prevailing view among the medical profession is that every tumor growth is essentially a surgical disease. Toxic adenoma having been recognized as a true tumor growth, except by a few dissen-

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<sup>67</sup> Bram, I. Goiter, Nonsurgical Types and Treatment, New York, The Macmillan Company, 1924, pp. 218 and 269.

ters, logically must, as soon as the diagnosis is made, be referred by every conscientious internist to the surgeon for immediate removal of the tumor, which is the cause of the toxic symptoms

**Radiotherapeutic** There prevails an inadequate familiarity with the achievements of roentgen therapy and radium in the treatment of neoplastic conditions in general, and thyroid neoplastic conditions in particular

*The Response of the Roentgen Therapists*—In 1902, when the technic of roentgen therapy was in its earliest infancy, Williams<sup>68</sup> of Boston was the first to report "I am using the x-rays for treating Parry's or Graves' disease, and thus far with encouraging results. The glands have diminished in size, and the general condition of the patients has improved."

Mary D., 26 years of age. Right lobe of thyroid gland 2x4 cm., left lobe 5x8 cm. After five exposures of twenty minutes each, given at intervals of about four days, the right lobe was 1½x2 cm., the left lobe 3¼x4 cm., and her general condition was much improved.

Two years later in 1904, Charles H. Mayo<sup>69</sup> reported a series of severe cases of exophthalmic goiter in patients who were poor surgical risks, but who had improved greatly after roentgen treatment. The patients were subsequently operated on successfully, without the high mortality rate which obtained in the early years of such operations. The roentgen technic carried out by Mayo<sup>70</sup> was as follows: "The x-ray is applied over the gland for as many times as is sufficient to discolor or even burn the skin. This treatment is given until the general condition is improved and the operation is considered safe." Surely no experienced radiotherapist in recent years ever recommended such strenuous skin treatment in cases of exophthalmic goiter as Mayo did then. It is strange, therefore, that one fails to find any mention of those perithyroid adhesions which are often advanced by surgeons as one of the chief objections against resorting first to roentgen treatment in cases of exophthalmic goiter before subjecting the patient to the risks of an operation.

Several months later, in 1905, another noted American surgeon, Carl Beck<sup>71</sup> of New York, reported the value of roentgen therapy not

68 Williams, F. H. *The Roentgen Rays in Medicine and Surgery*. New York, The Macmillan Company, 1902, p. 679.

69 Mayo, C. H. *Thyroidectomy for Exophthalmic Goiter, Based upon Forty Operative Cases*, M. Rec. 66:734, 1904.

70 Mayo, C. H. *Goiter: Its Surgical Treatment Based on Four Hundred and Seventy-five Cases, Collected papers by the staff of St. Mary's Hospital, Mayo Clinic, 1905-1909*, p. 446.

71 Beck, C. *Ueber die Kombination von Excisions- und Roentgen-Therapie bei Morbus Basedowii*, Berl. klin. Wchnschr. 42:593, 1905.

only as a preoperative measure in cases of exophthalmic goiter in patients who were poor surgical risks, but also as a postoperative measure in patients on whom thyroidectomy had been performed and who failed to be benefited by the operation. So impressed was he with the favorable results of roentgen treatment in postoperative cases that he subjected a number of patients preoperatively to this treatment and kept delaying the use of the skilled surgeon's scalpel until it was found no longer necessary, the patients having recovered under the roentgen treatment. In subsequent studies,<sup>72</sup> in 1908 and 1909, he reported his results and then formulated his indications for roentgen therapy in treatment of patients with exophthalmic goiter.

1 In cases with moderate enlargement of the thyroid gland, irradiation only is advocated, without an operation. Thirty-six cases, or 72 per cent of his series of fifty patients, were thus successfully treated.

2 In cases in which marked enlargement of the thyroid gland occurs, partial excision followed by roentgen treatment is the method of choice.

3 In cases in which the patients have severe symptoms and are poor surgical risks, preoperative irradiation is to be used until the patient improves sufficiently to endure the risks of an operation.

The favorable results of these three American pioneers quickly paved the way for the adoption of roentgen treatment in cases of exophthalmic goiter throughout the entire world. And, in 1915, when Ludin<sup>73</sup> of Basel collected from the literature 208 publications dealing with roentgen treatment of exophthalmic goiter, every civilized country on the globe was well represented. The consensus of opinion of the majority of these investigators was that with properly applied technic and sufficient clinical experience as good results can be achieved by roentgen treatment as by surgical intervention.

With improvement in surgical technic the mortality was gradually lowered in some clinics, but even at the present day there is a surgical mortality. Moreover, not every patient who recovers from the immediate dangers of the operation is cured at once, as is believed in both lay and medical circles. On the other hand, with improvement in roentgen technic and greater clinical knowledge in the treatment of this disease, a number of roentgen therapists have reported from 75 to 100 per cent success in the treatment of their patients. Although every roentgen therapist has not been as fortunate in his results, yet a recent

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72 Beck, C. Partial Thyroidectomy Combined with Roentgen-Therapy in Basedow's Disease, *Grad M. J.*, 1908, vol. 25, Struma u. Morbus basedowii und die Behandlung dieser Krankheiten mittels Röntgenstrahlen, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 15: 63, 1910.

73 Ludin, M. Die Behandlung der Strumen und des Morbus basedowii mit Röntgenstrahlen *Centralbl. f. d. Grenzgeb. d. Med. u. Chir.* 18: 205, 1914-1915.

review of the literature by Krause,<sup>74</sup> based on hundreds of carefully examined individual reports, places the average successful results at 82 per cent, practically the same figures as given by a careful analysis of the surgical results

Having obtained such favorable results from roentgen therapy in the treatment of patients with exophthalmic goiter in whom the clinical course of the disease is usually more severe and the pathologic involvement of the gland more diffuse and extensive than in toxic adenoma, one should therefore have expected even better results in toxic adenoma than in exophthalmic goiter. Indeed, it has been the experience of roentgen therapists that in the milder or formes frustes of exophthalmic goiter, among which unwittingly many cases of toxic adenoma must have been included, the results are much more favorable than in the outspoken cases of the disease. Unfortunately, a careful review of the literature fails to reveal a single publication especially devoted to the results of roentgen treatment of toxic adenoma. Only an occasional casual remark is found stating either that toxic adenoma responds more favorably than straightforward exophthalmic goiter or that in a few cases of toxic adenoma the results were not favorable.

Why has roentgen therapy failed to come forward with an authoritative, informative answer in toxic adenoma as it has done in hundreds of publications on exophthalmic goiter? The answer is that the roentgen therapist is almost entirely conditioned in the type of cases he is called on to treat by the decision of his medical or surgical colleagues, and both of these have decided that as soon as a diagnosis of toxic adenoma of the thyroid is made the case becomes at once surgical.

But are the indications for surgical intervention always greater in cases of toxic adenoma than in cases of exophthalmic goiter? Are the phenomena of mechanical pressure in toxic adenomas so frequent and severe that from the outset of their characteristically slow growth and development these tumors are unsuitable and unamenable to roentgen therapy? If the toxicity, as has been granted by both surgeons and internists, is of slower development and less in degree than in exophthalmic goiter, are the pressure phenomena the chief contraindications to roentgen therapy? If so, one should frankly formulate contraindications along these more rational lines than merely make an arbitrary statement. Toxic adenoma is essentially a surgical disease. I shall then consider the efficiency of roentgen therapy to cope with the compression phenomena of toxic adenoma and decide by actual study of a series of such cases whether these contraindications are valid or not. I do know however from a study of the literature and my own obser-

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74 Krause P. Die Röntgentherapie der Basedowschen Krankheit. Strahlentherapie 27 393, 1927-1928

vations that in toxic adenoma as in exophthalmic goiter it is most frequently, if not invariably, the toxic and not the compression phenomena that decide the issue of the case. Moreover, I do know that in cases of malignant tumors of the thyroid gland where invasive growth and compression phenomena are a much greater menace than in toxic adenoma of the thyroid, roentgen and radium therapy have yielded striking results. "Indeed," as stated in a recent publication,<sup>75</sup> "the results of radiotherapy in primary malignant tumors of the thyroid seemed so encouraging that a number of observers (Perthes,<sup>76</sup> Schadel,<sup>77</sup> Holfelder,<sup>78</sup> Holzkecht<sup>79</sup> and others stressed the superiority of radiotherapy over surgical intervention in treatment of fully developed thyroid cancer. Hence, I feel confident that with proper technic roentgen therapy should have yielded favorable results in toxic adenoma of the thyroid. I shall, however, not indulge in any further theoretical discussions what might have been accomplished by judicious roentgen therapy, but will proceed to present what has been accomplished by radium in the treatment of toxic adenoma of the thyroid.

*The Response of the Radium Therapists*—In a recent study,<sup>80</sup> the literature was reviewed and a series of cases reported which "incontestably prove the value of radium in the treatment of Graves' disease. Clinical cure of a lasting kind has been obtained not only by implanting radium interstitially into the thyroid gland but equally as well by external applications of properly screened radium." Can similar results be achieved by radium therapy in toxic adenoma of the thyroid? The answer to this question forms the text of the subsequent part of this study.

#### RADIUM THERAPY

Encouraged by the brilliant therapeutic result achieved by the American surgeon, Abbe,<sup>81</sup> with the interstitial use of radium in a severe case of exophthalmic goiter in which a prominent surgeon had refused opera-

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75 Ginsburg, S. Bone Metastasis in Thyroid Tumors. Early Diagnosis and Radiotherapy, *Am J Roentgenol* **18** 203, 1927

76 Perthes, J. Zur Biologie und Klinik der Rontgentherapie der chirurgischen Krebse, *Strahlentherapie* **15** 695, 1923

77 Schadel, W. Ueber Struma maligna, *Munchen med Wchnschr* **69** 1282, 1922

78 Holfelder, H. Die Erfahrungen mit der Rontgentherapie der Malignen Tumoren an der Schmiedenschen Klinik, *Strahlentherapie* **15** 715, 1923

79 Holzkecht, G. Schilddrusen Karzinom und Rontgenbestrahlung, *Wien klin Wchnschr* **38** 419, 1924

80 Ginsburg, S. Radium Treatment of Exophthalmic Goiter, to be published

81 Abbe, R. Exophthalmic Goiter Reduced by Radium, *Arch Roentg Ray* **9** 214, 1904-1905

tion, Wickham and Degrais,<sup>82</sup> in 1906, proceeded to use radium in the treatment of a patient with toxic adenoma of the thyroid. Instead of following Abbe's technic, they used a method which may be appropriate in the treatment of superficial skin lesions, but which was by no means calculated to affect a bulky toxic adenoma of the thyroid. Nevertheless, the result was much better than could have been anticipated. Not only did they obtain a reduction in the toxic manifestations of the disease but also a shrinkage of the adenoma.

With improvement in radium technic, it was readily demonstrated that highly favorable results can be achieved by the use of radium in cases of toxic adenoma just as well as in cases of classic exophthalmic goiter. What efficient radium therapy has achieved in the treatment of patients with exophthalmic goiter has been reviewed in a recent study. A careful perusal of the literature fails to show a single publication devoted especially to radium treatment of toxic adenoma. However, in the reports of Aikins,<sup>83</sup> Loucks,<sup>84</sup> Bower and Clarke<sup>85</sup> and Larkin,<sup>86</sup> many cases of toxic adenoma of the thyroid are mentioned in which treatment with radium was successful. Not only were the toxic symptoms relieved but the compression phenomena were also entirely removed.

Nevertheless, while radium treatment has been successful in many cases of toxic adenoma of the thyroid, the total number reported to date is still comparatively small. Hence, it will be of sufficient interest to submit a detailed report of the following eight cases from the radium clinic of the Beth Israel Hospital, during the years of from 1924 to 1927.

CASE 1—A woman, aged 44, married, was admitted to the radium clinic of Beth Israel Hospital on Feb. 3, 1925, complaining of weakness, irritability, progressive loss in weight, sleeplessness, enlargement in the right cervical region, hoarseness and cough of three years' duration. The previous history was unimportant. The present illness had its onset in 1921 with progressive weakness, anorexia and constipation. During the year previous to presentation at the clinic irritability, progressive loss in weight, sleeplessness and enlargement in the right cervical region had occurred, lately slight hoarseness and cough had developed.

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82 Wickham, L., and Degrais, P. Radiumtherapie, J. B. Bailliere et fils, Paris, 1909.

83 Aikins, W. H. B. Radium in Toxic Goiter, *Am. J. Roentgenol.* **7**: 404, 1920.

84 Loucks, R. E. Radium Treatment of Toxic Goiter with Metabolic Deauctions, *Am. J. Roentgenol.* **10**: 767, 1923, Radium Treatment of Thyrotoxicosis, *Radiology* **4**: 473, 1925, Clinical Evidence of Thyrotoxic Control after Radium Therapy, *Am. J. Roentgenol.* **18**: 509, 1927.

85 Bower, J. O., and Clarke, J. H. Action of Radium on Diseased Thyroids in Man, *Am. J. Roentgenol.* **10**: 632, 1923.

86 Larkin, A. J. Radium in Twenty Cases of Hyperthyroidism. *Illinois M. J.* **49**: 468, 1926.



Physical examination revealed in the right lobe of the thyroid gland just above the sternoclavicular junction an oval mass, 4 by 4 by 3 cm in diameter, firm in consistency, moving with deglutition. The rest of the thyroid gland was apparently not enlarged. Bruit and thrill were absent. The heart and lungs were normal. The basal metabolic rate was plus 8.

The diagnosis was toxic adenoma of the thyroid.

Radium treatment was instituted. Between Sept 14 and 27, 1925, the patient received 3,000 mg hours of radium with the block (fig 1) at 3 cm distance over the tumor mass and another dosage of 3,000 mg hours over the upper sternal region.

The result was the shrinkage of the adenoma to 3 by 3 by 2 cm in size and subsidence of constitutional symptoms. At the last examination on May 5, 1927, the adenoma was shown to be stationary in size and the patient free from any toxic symptoms.

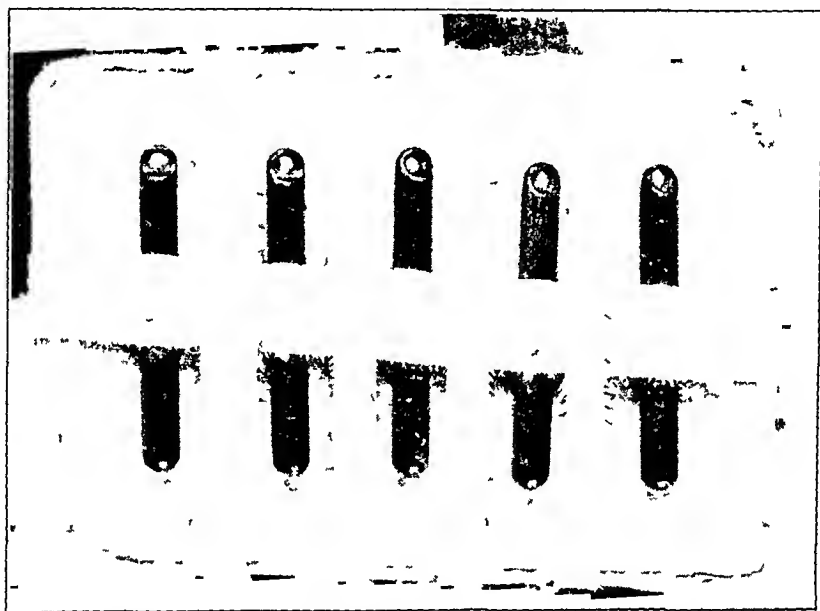


Fig 1—Radium block. The radium block is made of balsa wood. Its dimensions are 7 by 5 by 3 cm. It is covered by adhesive plaster. Several layers of gauze are interposed between it and the skin to serve as a cushion and to absorb perspiration. The distribution of the radium capsules is shown. Each brass capsule, 1 mm thick, contains from 10 to 25 mg of radium in the form of standard steel needles, according to indications. The block is strapped in place by means of adhesive plaster and reinforced with a bandage, 3,000 mg hours constitute an erythema dose.

*Comment*—Five important lessons taught by this comparatively simple case are

1. Fairly marked, progressive, toxic constitutional symptoms may be present for a period of four years with a comparatively small toxic adenoma measuring 4 by 4 by 3 cm. This emphasizes again the important clinical observation that the degree of the enlargement of the thyroid in toxic goiter does not run parallel with the toxic manifesta-

tions. A bulky adenoma of ten, twenty or even forty years standing may exist without constitutional symptoms. On the other hand a small or even clinically impalpable toxic adenoma may give rise to fairly marked toxic constitutional symptoms.

2. Fairly marked toxic constitutional symptoms may be present for years with a comparatively low basal metabolic rate. Although the basal metabolic rate is one of the most reliable aids in gauging the degree of severity in cases of toxic goiter, every experienced worker in thyroid pathology knows that the severe cases may be at times accompanied by a low basal metabolism. In this machine-made age when mechanical aids in diagnosis are frequently given the precedence over expert clinical observation and keen cerebration, the low basal metabolism associated with fairly marked toxic clinical symptoms in this case is a new reminder to correlate carefully all clinical and laboratory data and to be guided primarily by careful clinical diagnostic criteria.

3. The prompt response of toxic adenoma to a single erythema dose of radium treatment in this case may be noted. The prompt improvement which was striking in this case was not only exceedingly gratifying to the patient, but also taught the radium therapist the important lesson that in radium one has a bloodless, safe, efficient physical agent that can vie successfully with the surgeon's scalpel in its attack on toxic adenoma of the thyroid.

4. The persistence of the clinical cure nineteen months after a single radium treatment is another important consideration. A cure induced even by a single dose of radium may be lasting.

5. The shrinkage of the adenoma from 4 by 4 by 3 cm. to 3 by 3 by 2 cm. sufficed to cause the disappearance of all toxic constitutional symptoms. Evidently complete disappearance of a toxic adenoma is not necessary to induce clinical cure in toxic goiter. A small moderate-sized, or even a bulky adenoma may be present without necessarily inducing toxic symptoms.

CASE 2—*History*.—Jacob B., aged 75, a porter, first came under observation at the radium clinic of Beth Israel Hospital on Feb. 5, 1925. His chief complaints were irregular enlargement of the neck, nervousness, weakness, loss in weight, dyspnea and palpitation on exertion, all of five years' duration.

In the summer of 1920 the patient noticed a painless lump, the size of a walnut, in the right lower cervical region. A few weeks later a similar lump was felt in the left lower cervical region. Slowly but progressively the lumps continued to increase in size and were followed by the development of dysphagia, choking sensation in the throat, nervousness, headache, weakness, palpitation, tachycardia and dyspnea on exertion, marked tremor of the hands and a loss of 30 pounds (13.6 Kg.) in weight. In July, 1924, a basal metabolic determination showed plus 25 per cent. During the latter part of the same year he was given several applications of small doses of radium to the thyroid with apparent temporary improvement.

*Physical Examination*—Examination presented a well developed old man, looking much younger than the stated age. In his entire bearing there was marked nervousness and tremulousness. His face was suffused with a dusky flush. He was undernourished but not cachectic. Ocular signs of exophthalmic goiter were absent. The thyroid gland showed a large tumor mass in each lateral lobe (fig 2A). The left tumor mass was smooth, oval, elastic, nontender and movable. Its dimensions were 6 by 5 by 3 cm. The mass in the right lobe of the thyroid was much harder but was not nodular nor irregular. It was freely movable, not tender on palpation and measured 9 by 7 by 5 cm. The circumference of the neck through the seventh cervical vertebra and the center of the tumor masses was 41 cm. Bruit and thrill were absent. The heart was slightly enlarged. The sounds were distant but regular. The second aortic sound was accentuated, but murmurs and irregularities were not detected. The blood pressure was 170 systolic and 65 diastolic. The upper extremities showed a marked coarse tremor.



Fig 2 (case 2)—A, toxic adenoma of the thyroid in a man, aged 75. Moderately severe toxic symptoms endured for five years. The basal metabolism was plus 25. The circumference of the neck was 40 cm (July, 1924; before radium treatment). B, four months after radium treatment. There was relief of thyrotoxic symptoms, including disappearance of auricular fibrillation. Basal metabolism was normal. The circumference of the neck was reduced from 40 to 35 cm, with a simultaneous gain in weight (January, 1926).

*Laboratory Data*—Roentgen examination of the chest showed slight enlargement of the cardiac shadow and a widening of the aortic arch. Electrocardiographic tracings were normal. The blood and urine were normal. The basal metabolism was plus 12 per cent. The diagnosis was toxic adenoma of the thyroid.

*Course Under Observation Before Radium Treatment*—On Feb 20, 1925, without any other discoverable cause except the condition of the thyroid, the patient developed auricular fibrillation. He was immediately ordered to rest in bed and was placed on moderate doses of digitalis. He improved gradually and about the middle of April, 1925, the heart action became regular. The improvement, however, was only temporary in duration, and the auricular fibrillation recurred with persistency of all the thyrotoxic symptoms.

*Course Under Radium Treatment*—During the early part of May 1925 he was given a dosage of 2,000 mg. hours of radium with the block at 3 cm. distance over each adenomatous mass. Within a few weeks there was moderate improvement in constitutional symptoms and a shrinkage of the adenomas. On June 18, 1925, auricular fibrillation was still present, but the patient felt stronger and the circumference of the neck showed a reduction from 41 to 36.5 cm. During the latter part of August, 1925, he was given 2,300 mg. of radium with the block at 3 cm. distance over the thymus region. This treatment was followed by further improvement in his general condition and a gain of 20 pounds (9 Kg.) in weight. Examination in January, 1926, found him in excellent condition. The auricular fibrillation had disappeared, and only an occasional extra systole was present. The circumference of the neck had shrunk from the original 41 to 35 cm. (fig. 2 B).

Further radium treatment was not given. The last examination in September, 1928, more than three years after the last radium treatment, showed the result unchanged.

*Comment*—Whether this patient was too old for surgical intervention, I do not undertake to judge. I feel grateful, however, to his physician who forbade operation. This gave an opportunity to use radium therapy and to demonstrate the fact that in operations on patients who are poor surgical risks it is no longer necessary to "let nature take its course." The efficiency of radium put to the test in this case produced an excellent result practically amounting to a cure. The persistence of excellent results four years after treatment with radium was first stated stresses the important lesson to the medical profession that the surgeon's scalpel is not the only means of attack against a toxic adenoma of the thyroid. Radium therapy efficiently used may give as good or even better result than surgical intervention without its attendant operative mortality, especially in the aged and feeble sufferers of toxic goiter.

*CASE 3—History*—Rose W., aged 14, was referred to the radium clinic of Beth Israel Hospital in January, 1926, by Dr. B. Rosenbluth of New York, because of goiter, nervousness, irritability, loss in weight and insomnia, all of four months' duration. In October, 1925, four months before admission, the presence of a goiter was detected by the school nurse. The goiter kept fluctuating in size, but not until three months after its discovery were there any toxic symptoms noted.

*Physical Examination*—Examination showed a well nourished and developed girl, aged 14, who weighed 96 pounds (43.5 Kg.). Her face was flushed. Her eyes were somewhat prominent, but exophthalmos was not definitely present. There were no other ocular signs of exophthalmic goiter. The thyroid gland showed a diffuse enlargement with predominant involvement of the isthmus and right lobe. The right lobe was firmer than the rest of the gland and felt distinctly nodular. A slight bruit was detected over the right lobe. Thrill was absent. The circumference of the neck through the seventh cervical vertebra and the midthyroid region measured 33.5 cm. The heart showed moderate enlargement. The pulse rate was 140 per minute in the recumbent posture. Murmurs and irregularities were absent. The blood pressure was 120 systolic and 78 diastolic. The results of the rest of the examination were negative.

*Laboratory Data*—Roentgen examination of the chest showed cardiac enlargement. Electrocardiographic tracings showed simple tachycardia, left ventricular predominance and the T wave inverted in lead 3. The blood and urine were normal. The basal metabolic rate was plus 14 per cent.

The diagnosis made was toxic adenoma of the thyroid.

*Course Under Radium Treatment*—Radium treatment was started in February and was completed in April, 1926. The left lobe of the thyroid and the thymus received 2,300 mg. hours of radium each with the block at 3 cm. distance, while the right lobe of the thyroid was given 3,000 mg. hours. Improvement in subjective symptoms was noted at the end of April. Within five weeks after the first fractionated dose of radium was given her weight increased from 92 (41.7 Kg.) to 104.5 pounds (47.2 Kg.). The circumference of the neck was reduced to 33 cm. The heart showed only slight acceleration. Reexamination in February, 1927, found the patient completely free from any subjective complaints. She had gained 20 pounds (9 Kg.) in weight since her first admission to the radium clinic. Her neck had shrunk from the original 33.5 to 32.5 cm. There was still a slight bruit over the right lobe of the thyroid. Restudy with special reference to the need of any further radium treatment was suggested, but the patient considered herself well and saw no need to follow the recommendation. At the time of the last examination in August, 1928, the condition was practically unchanged.

**CASE 4—History**—Rebecca S., aged 51, was admitted to the radium clinic of Beth Israel Hospital, March 9, 1926, complaining of a lump in the neck, nervousness, irritability, undue emotionalism, tremor, sleeplessness and loss in weight of five years' duration.

In 1921, five years before admission, her sister called her attention to the presence of a lump in the neck. Shortly thereafter she began to suffer from tremor, undue emotionalism, irritability, loss in weight and insomnia. During the past four years she consulted several physicians who diagnosed toxic goiter and prescribed internal medication, without any definite improvement in her symptoms.

*Physical Examination*—Examination showed a well developed and nourished middle-aged woman weighing 128 pounds (57.1 Kg.). She appeared nervous and apprehensive. Her eyes were brilliant and presented a slight von Graefe's sign, but definite exophthalmos was absent. The tongue was slightly tremulous, the fingers markedly so. The thyroid gland showed an irregular enlargement of the isthmus and the left lobe. The right lobe was barely palpable. The mass was partly retrosternal and much firmer than normal. The skin was movable over it, but the growth seemed to be adherent to the deep cervical tissues. The circumference of the neck through the seventh cervical vertebra and the midthyroid region measured 35.5 cm. The heart was slightly enlarged. The pulse rate was 120 per minute. Murmurs and irregularities were absent. Blood pressure was 130 systolic and 70 diastolic. The abdomen was moderately distended. The liver was enlarged and extended 5 cm. below the costal margin. The spleen and kidneys were not palpable. The lower extremities did not show edema.

*Laboratory Data*—Roentgen examination of the chest showed a substernal thyroid with deviation of the trachea to the right. Electrocardiographic tracings revealed a simple tachycardia. The blood and urine were normal. The basal metabolic rate was plus 14 per cent.

The diagnosis was toxic adenoma of the thyroid, partly retrosternal, with deviation and compression of the trachea (fig. 3A).

*Course Under Radium Treatment*—During the week of April 22 to 29, 1926, a dose of 3,000 mg. hours of radium with the block at 3 cm. distance was given.

over the center of the mass. The result of this treatment was moderate improvement in constitutional symptoms and a shrinkage in the size of the neck from 35.5 to 33 cm. On June 9, 1926, without any increase in subjective complaints, a marked tachycardia was detected. Electrocardiographic examination revealed auricular flutter. The auricular rate was 300, the ventricular 150 giving thus a 2:1 heart block. How long this attack had lasted is unknown, for the case was



Fig. 3 (case 4)—*A*, toxic adenoma of the thyroid, partly retrosternal, in a woman, aged 51. Moderately severe toxic symptoms were endured for five years. The circumference of the neck was 35.5 (March, 1926, before radium treatment). *B*, thyrotoxic symptoms were relieved after radium therapy. The circumference of the neck was reduced from 35.5 to 31.75 cm. *C*, further reduction of the circumference of the neck from the original 35.5 to 30.75 cm, and a gain in weight of 11 pounds (5.4 Kg.) since admission to the radium clinic (February, 1928).

an ambulatory clinic case and the patient was not reexamined electrocardiographically until June 23, 1926. Auricular flutter was no longer present then; only a simple tachycardia persisted, and the P wave in leads 2 and 3 was high and notched.

In the meanwhile, commencing on June 19 and ending on July 20, another course of radium treatments was administered over the mass and over the upper retrosternal region. The result of this treatment was extremely gratifying. On July 27, 1926, only one week after the last fractionated dose of radium was given, the patient felt greatly improved in all her symptoms. She now felt strong enough to perform all her household duties without any undue fatigability. She felt fairly well until the fall of 1927, when a mild recrudescence occurred as the result of emotional stresses. A single course of radium treatments again controlled her symptoms. On the last examination in July, 1928, she was in fair health with marked shrinkage in size of the adenoma, and no intrathoracic compression symptoms were noted. The heart rate was only slightly above normal. Her basal metabolism rate was normal. The skin showed no atrophy or telangiectasis (fig 3 B).

*Comment*—The result achieved in this case by radium treatment reveals to every unbiased student of toxic adenoma of the thyroid that surgical intervention is no longer the only method of relief in dealing with this serious problem. This was a patient who had an outspoken condition of toxic retrosternal adenoma, of the thyroid with intra-thoracic compression phenomena. At one time she developed an attack of auricular flutter with a rate of 300 and 2:1 heart block. Yet under radium treatment the thyrotoxic symptoms were controlled, the compression phenomena were relieved, the adenoma was shrunk to a fraction of its former size, and the patient was restored to a life of comparative usefulness and comfort without having been subjected to the dangers of an operation.

*CASE 5—History*—Yetta K., aged 48, was referred to the radium clinic of Beth Israel Hospital, Dec 7, 1926, by Dr. Max Weitzen of New York, complaining of symptoms of one year's duration consisting of progressive asthenia, palpitation, dyspnea, emotional instability, diarrhea, loss in weight, swelling of the neck, enlargement of the veins of the neck and of the upper part of the chest, cough, hoarseness and prolapsus ani.

In 1917, she developed weakness and palpitation on exertion. On examination, a "cystic" swelling about the size of a pigeon's egg was discovered in the right lobe—and a similar swelling about the size of an olive in the left lobe—of the thyroid gland. In July, 1917, the larger mass only was enucleated. The patient improved rapidly after the operation and felt apparently well until the end of 1925.

In December, 1925, following a period of emotional stress, she developed progressive asthenia, palpitation even at rest and marked dyspnea on exertion. She became irritable and unduly emotional, was annoyed by apparently causeless diarrheal stools and lost weight progressively. Six months later, in the summer of 1926, she noticed swelling of her neck and enlargement of the veins of the neck and the upper part of the chest. Her condition gradually grew worse, and she was finally referred to the radium clinic of Beth Israel on Dec 7, 1926.

*Physical Examination*—Physical examination showed a middle-aged woman depressed, worn, slightly anemic and undernourished, weighing 118 pounds (53.5 Kg). Exophthalmos and other ocular signs were absent. The tongue was tremulous. In the lower right cervical region there was a transverse, supple, non-adherent scar. The superficial veins over the lower anterior part of the neck and

the upper part of the chest were dilated (fig 4 *A*), more markedly on the left than on the right. The thyroid gland showed a diffuse, irregular enlargement more marked on the left than on the right. Consistency of the gland was firmer than normal. Bruit and thrill were absent. The circumference of the neck through the seventh cervical and the midthyroid region measured 34.5 cm. The heart was not enlarged. The pulse rate was 124 per minute. Murmurs and irregularities were absent. The blood pressure was 130 systolic and 80 diastolic. The results of the rest of the examination were essentially negative.

*Laboratory Data*—Roentgen examination of the chest showed deviation and compression of the trachea to the right by a substernal thyroid. Electrocardiographic tracings showed simple tachycardia and the P wave notched in leads 2 and 3. Examination of the blood revealed red blood cells, 3,300,000, hemoglobin content

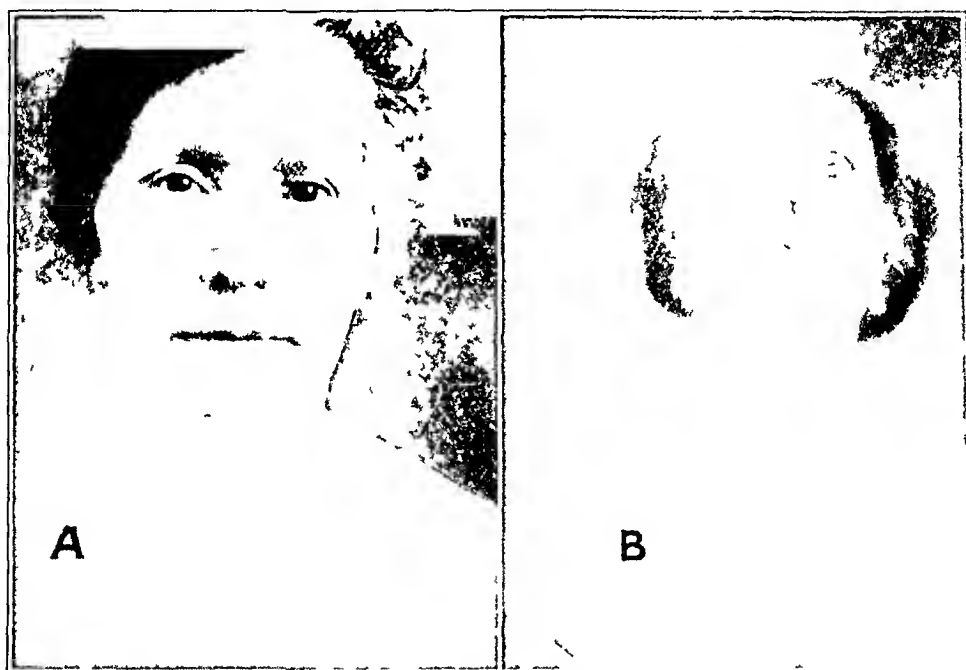


Fig 4 (case 5) —*A*, postoperative recurrent toxic adenoma of the thyroid with mediastinal compression phenomena, as evidenced by enlarged veins over the neck and the upper anterior part of the chest. Moderately severe toxic symptoms endured for one year. The patient did not respond to medical treatment in addition to several roentgen treatments. The circumference of the neck was 34.5 cm (December, 1926, before radium treatment). *B*, two weeks after the last application of radium. Marked improvement in constitutional symptoms resulted. There was a drop in basal metabolism of from plus 58 to plus 6, and a gain in weight of from 118 to 129 pounds (53.5 to 58.5 Kg). With the shrinkage of the neck from 34.5 to 32.5 cm, dilatation of the veins over the neck and the anterior part of the neck was no longer present (July 28, 1927, after radium treatment).

70 per cent, white blood cells, 5,500, polymorphonuclears 50 per cent, large lymphocytes, 5 per cent, small lymphocytes, 45 per cent. The urine showed a trace of albumin and a few hyaline casts. The basal metabolic rate was plus 58 per cent.

*Course Under Radium Treatment*—In January 1927, 6,090 mg hours of radium with the collar (fig 8) at 3 cm distance were given to the thyroid region and



3,700 mg hours with the block at 3 cm distance to the upper retrosternal region. The result was prompt improvement in subjective symptoms and a shrinkage of the neck from 34.5 to 33 cm. In the early part of March, 1927, two months after the first radium treatment had been given, her weight increased from 118 (53.5 Kg) to 125 pounds (56.7 Kg) but the tachycardia persisted. A restudy of the basal metabolism showed plus 58 per cent. Accordingly, at the beginning of June, 1927, radium treatment was repeated. The improvement this time was even more marked than after the first series of treatments. On July 20, only one week after the last fractionated dose of radium was given, her basal metabolism had dropped from plus 58 to plus 6 per cent. She felt much stronger. Her weight had increased to 129 pounds (58.5 Kg). The pulse ranged between 84 and 90. The blood pressure was 125 systolic and 80 diastolic. The circumference of the neck showed a further reduction from the original 34.5 to 32.5 cm. The improvement was not confined, however, merely to the thyroid growth in the neck. The intra-

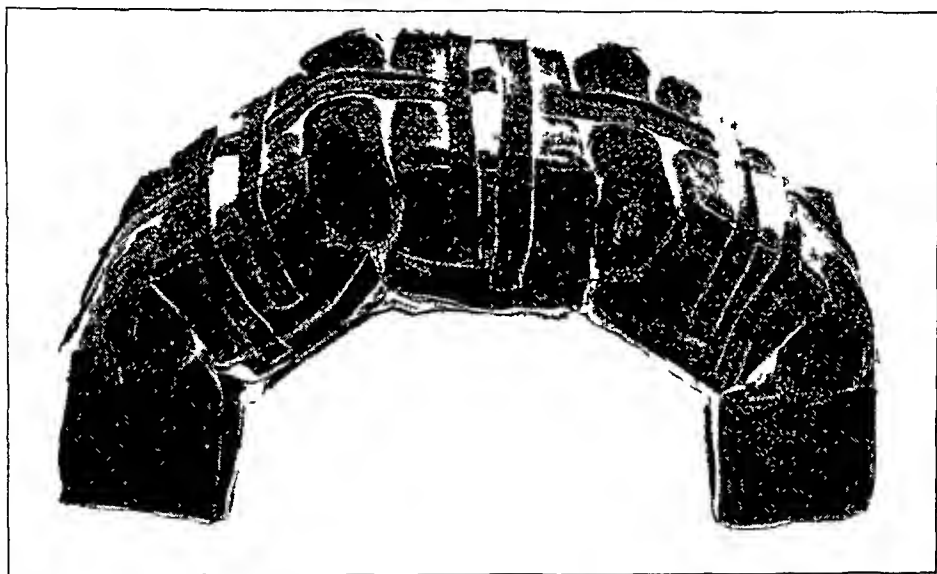


Fig 5—Radium collar. The radium collar is made of five blocks of balsa wood, each block measuring 5 by 3 by 3 cm. The blocks are held together by adhesive plaster. Their proper adjustment to the neck is obtained by pledgets of gauze. The distribution of the radium capsules is shown. Each brass capsule, 1 mm thick, contains from 10 to 25 mg of radium in the form of steel needles, according to indications. The collar is strapped in place by adhesive plaster and reinforced by a bandage, 6,000 mg hours constitute an erythema dose.

thoracic retrosternal adenomatous mass must have been similarly affected, for the dilatation of the veins over the neck and the upper anterior part of the chest was no longer present (fig 4 B).

Reexamination two months later showed that the patient was in good condition with a pulse rate of 72. She had been attending to her housework regularly. What is even more important, she had been subjected for almost two months to great emotional stress. One of her daughters had developed general sepsis and had been in a critical condition all this time. Moreover, during the same period her husband had succumbed to gastric cancer. Yet she stood well all these emotional stresses without any recrudescence of toxic symptoms. The last examination on

Aug 2, 1928, found the improvement persisting in spite of active abdominal symptoms from a pathologically diseased gallbladder with a large impassible stone demonstrated roentgenologically

*Comment*—The response to radium therapy in this case removes the chief objections to the treatment of toxic adenoma by radium. If such marked compression phenomena, as were present in this case can be removed by radium therapy, what contraindication then remains to its use in toxic adenoma of the thyroid?

*CASE 6—History*—Miss F. S. S., aged 40, a school teacher, was referred by Dr. D. A. Swick of New York on March 19, 1927 because of undue emotionalism, irritability, hoarseness, goiter, weakness, tachycardia, palpitation, diarrhea, loss in weight and sleeplessness of six years' duration. The present illness began six years prior to examination, in 1921, when she began to develop symptoms of thyrotoxicosis followed one year later by the appearance of a painless lump in the right side of the neck. Medical consultation led to a diagnosis of toxic goiter, and the patient was put through a regimen of rest, diet and internal medication. A brief period of improvement was followed by a prolonged relapse. And although during the years from 1924 to 1927 she improved spontaneously she was unable to resume her professional duties for more than a few hours a day and was frequently compelled to stay away from school for several days at a time.

When she was seen by me for the first time in March, 1927, she complained of all the symptoms enumerated.

*Examination*—Physical examination presented a well nourished and developed young woman with flushed face and slightly prominent and brilliant eyes. There was only a suggestive von Graefe's sign, but no definite exophthalmos in spite of clinically perceived thyrotoxic symptoms of six years' duration. The scalp was normal, and there was an abundant growth of hair. Her skin was moist and dermatographia was easily elicited. The teeth were in good condition. The tongue was coated, fissured and tremulous. The pharynx was slightly congested.

Examination of the thyroid gland revealed in the right lobe and isthmus a large oval, elastic mass measuring 10 by 6 by 4 cm. in size. The left lobe was slightly enlarged. The adenomatous mass was nontender, movable and not unduly vascular. Pulsation of the vessels in the neck was not increased. Bruit and thrill over the thyroid were absent. The circumference of the neck through the seventh cervical vertebra and the midthyroid region measured 36 cm. The transverse diameter was from 14 to 15 cm., the right vertical measured 6 cm., the left, 4 cm., the thickness of the right lobe was 4 cm., that of the left 2 cm.

The heart was not enlarged. There was a soft apical systolic murmur. The rate was 124 in the upright and 120 in the recumbent posture. The lungs did not show any abnormality. Results of the abdominal examination were negative except for a low median scar, the result of a gynecologic operation. There was moderate tremor of the fingers. The lower extremities were normal.

The basal metabolic rate was plus 29.

The diagnosis was toxic adenoma of the thyroid.

*Course Under Radium Therapy*—Between April 2 and 16, 1927 the patient was given 6,000 mg. hours of radium to the thyroid with the radium collar at 3 cm. distance and 3,000 mg. hours to the thymus region with the block at 3 cm. distance. The results were extremely gratifying. On May 7, only five weeks after the first fractionated dose of radium was applied and with a skin erythema

from the radium fully developed, she was subjectively free from symptoms. The pulse rate had dropped from 124 to 120 to 100 to 88. The circumference of the neck was reduced from 36 to 34.5 cm and the adenoma measured 9 by 6 by 3. On June 28, she felt entirely well. For almost two months she had been able to attend to her professional duties without any fatigue. The school authorities had noticed the favorable change and complimented her "for not being absent a single day during this term." Her pulse rate was from 84 to 90. The adenoma had shrunk from 10 by 6 by 4 to 7 by 6 by 3 cm. She was seen again in September, 1927, and was found clinically well. In July, 1928, I was informed by Dr. Swick that the condition remained unchanged. During the entire year, she attended regularly to her professional duties and felt entirely well.

*CASE 7—History*—Rose B., aged 28, referred to the radium clinic of Beth Israel Hospital on Feb. 8, 1927, by Dr. Charles J. Brim of New York, had rapid enlargement of the thyroid gland, loss of 30 pounds (13.6 Kg.) in weight, nervousness, tremor, palpitation, dyspnea, hoarseness, dysphagia, marked asthenia, anorexia, diarrhea, cough, nausea and vomiting and night sweats of three months' duration. The present illness began in 1919, when, shortly after the birth of her first child, she noticed a slight prominence of the anterior region of the neck. This enlargement gave rise to no local discomfort and apparently remained stationary in size until the fall of 1926. Simultaneously with the growth in the neck she noticed a tendency to nervousness, accompanied during the last two years by slight progressive loss in weight. In November, 1926, she had an incomplete abortion followed by curettage. Eight days later, she developed signs of pneumonia and was ill for four weeks. When the pulmonary condition was improving, she noticed that the growth in her neck was enlarging rapidly. Presently she began to suffer from headaches, blurring of vision, dryness of mouth and lips, choking sensation in the throat, throbbing of the vessels in the neck, tachycardia and palpitation, dyspnea on exertion, anorexia and nausea, diarrhea, asthenia, disturbed sleep, night sweats, tremor, nervousness and irritability. Within three months after the onset of her symptoms, she lost 30 pounds (13.6 Kg.) in weight.

In spite of these complaints, she struggled along to take care of her four children and her household duties. At last her strength gave way, and she consulted Dr. Brim, who had her referred to the radium clinic on Feb. 8, 1927.

*Examination*—Physical examination presented a young woman, nervous, restless, with a flushed face and prominent eyes, but without definite signs of exophthalmic goiter. There was a slight von Graefe's sign. Other ocular signs were absent. Her tongue was slightly tremulous, although the fingers showed marked tremor. The pharynx was slightly congested. The tonsils were moderately enlarged and congested and appeared diseased. There was slight visible pulsation of the carotid vessels.

Examination of the thyroid gland showed a diffuse enlargement with predominant involvement in the isthmus. A large area in the isthmus felt harder than the rest of the thyroid tissue and was suggestive of an adenoma surrounded by diffuse hyperplastic tissue. The gland was freely movable, both under the skin and over the underlying tissues. Thrill was absent although a bruit was present over the entire gland. The circumference of the neck through the seventh cervical vertebra and the midthyroid region measured 36 cm. The transverse diameter was 14 cm., the right vertical, 5 cm., the left vertical, 4 cm., the thickness of the right lobe was 3 cm., that of the left 2 cm. (fig. 6A).

Examination of the heart showed no enlargement, and the rate was 96 systolic and 100 diastolic. The apical sound was booming and the second aortic sound

was accentuated. Murmurs and irregularities were not detected. The blood pressure was 150 systolic and 60 diastolic. The lungs were normal.

Examination of the abdomen revealed the upper level at the fifth right interspace midclavicular line and the lower border 4 cm below the costal margin. The surface was smooth, the edge sharp and nontender. The upper level of splenic dullness reached the seventh interspace left midaxillary line; the lower border was palpable from 2 to 3 cm below the costal margin.

Results of rectal and vaginal examinations were negative.

*Laboratory Data*—Roentgen examination of the chest showed the cardiac shadow enlarged to both sides. Electrocardiographic tracings showed left ventricular preponderance and tachycardia. The urine was normal. Examination of the blood revealed red blood cells, 3,470,000, hemoglobins, 5 per cent, white blood cells, 7,100, polymorphonuclears, 44 per cent, large lymphocytes, 3 per cent, small lymphocytes, 51 per cent. The basal metabolism was plus 52 per cent.

The diagnosis was toxic adenoma of the thyroid with diffuse hyperplasia.



Fig 6 (case 7)—*A*, toxic adenoma of the thyroid in a woman, aged 28. Mild toxic symptoms ensued for almost eight years, severe toxic symptoms for three months. Basal metabolism was plus 52. The circumference of the neck was 36 cm (February, 1927, before radium treatment). *B*, four months after a single course of radium treatments to the thyroid region only. All toxic symptoms disappeared, and there was a great gain in weight. The pulse rate was 72. The basal metabolism was normal. The circumference of the neck was reduced from 36 to 33 cm (Sept 8, 1927, after radium treatment).

*Course Under Radium Treatment*—Commencing on April 26 and ending May 1, 1927, the patient received one continuous radium treatment with the radium collar at 3 cm distance over the adenoma as its center. The total dose delivered was 6,000 mg hours. The result was one of the most favorable I have ever observed in the treatment of toxic goiter by radium. Within one month after the single radium treatment was given she felt sufficiently improved to perform her household duties without undue strain. She had lost almost all of her symptoms and had gained 3 pounds (1.4 Kg) in weight while the circumference of her neck was reduced from 36 to 33 cm. Her pulse rate dropped to 84 per minute. A basal metabolic determination showed plus 4. Reexamination on July 5, 1927,

showed a pulse rate of 72 and blood pressure readings 110 systolic and 60 diastolic, a drop of forty points in the systolic pressure without any change in the diastolic. With the shrinkage in the diffuse hyperplasia of the thyroid gland a single, discrete, hard tumor mass could be distinctly outlined in the isthmus and right lobe of the thyroid (fig 6 B).

The patient has been kept under observation since, and at no time has she shown any recurrence of toxic symptoms. The last examination in June, 1928, showed her weight to have returned to 155 pounds (70.3 Kg.), the best she ever weighed before the onset of her toxic symptoms.

*Comment*—Striking results from a single radium treatment as shown in this case are seldom encountered in the clinically classic cases of diffuse hyperplastic toxic or exophthalmic goiter, while in cases of toxic adenoma more than once has a similar response been observed. Nor is the constitutional reaction from the application of radium as marked in the average case of toxic adenoma as it is in the diffuse involvement of exophthalmic goiter. Evidently the discrete involvement of the thyroid represented by a single toxic adenoma is a lesion favorable to attack not only by surgical intervention but by radium therapy as well.

*CASE 8—History*—Beckie O., aged 32, was referred to the radium clinic of the Beth Israel Hospital on March 8, 1927, by Dr. Max Weitzen of New York. Her condition consisted of goiter, nervousness, tremor of the hands, recurring attacks of mental depression, flushes of heat, night sweats, paroxysmal attacks of cough, dyspnea and palpitation on exertion, headache, irritability, emotionalism and loss of 32 pounds (14.5 Kg.) in weight. The goiter had been present twenty-six years, while the toxic symptoms had endured seventeen years.

The mother and one sister had had enlargement of the thyroid gland for a number of years, apparently not accompanied by any constitutional symptoms.

At the age of 6 years the patient became aware of the presence of a lump in the lower part of the center of the neck, which ever since its first appearance had remained practically stationary in size. In 1910, when the patient was 15 years of age, she developed nervousness, tremor of the hands and recurring attacks of abdominal pain. After medical measures had been tried for a time with complete failure, she was advised to undergo appendectomy for a supposed chronic appendicitis. One year later, the appendix was removed, but the patient's symptoms remained unrelieved. In 1917, after the birth of her first child, she developed an attack of severe melancholia which lasted for a year and a half. Milder attacks had been recurring ever since. In 1925, two years before admission to the radium clinic, she suffered an acute grippal infection which left her with a burning sensation in the throat and noises in both ears. Her nervous symptoms gradually increased in severity. She had flushes of heat and night sweats. In January, 1926, a tonsillectomy was performed for the exceedingly annoying condition of the throat. Relief failed to follow. Instead, since the tonsillectomy she has had frequent paroxysmal attacks of cough and expectoration. Her appetite was poor. She has lost 32 pounds (14.5 Kg.) in weight during the past several years. She was extremely emotional and irritable and easily became depressed. During the past fourteen months, following the tonsillectomy, marked asthenia has been the predominant and most distressing symptom.

She was treated ineffectually by several physicians and was finally referred to the radium clinic of the Beth Israel Hospital on March 8, 1927.

*Examination*—What struck one especially, during the first glance at the patient was the exceedingly woe-begone melancholic expression on the face (fig 7 A) which was not subdued by the marked flush in her cheeks. There was no exophthalmos in spite of a history of seventeen years of thyrotoxic symptoms and in spite of the unmistakable mental manifestations which have been stressed by some observers as an important diagnostic feature that distinguishes exophthalmic goiter from toxic adenoma of the thyroid.

Examination of the pharynx failed to reveal sufficient cause for the excessively distressing throat symptoms. Only a slight congestion was present. The tonsils were entirely absent, having been successfully enucleated without any apparent benefit to the patient. The tongue was not tremulous although the hands showed a fine tremor.

Examination of the thyroid gland showed an irregular nodular enlargement especially of the isthmus. The gland was firmer than normal but was freely movable. Bruit and thrill were absent. The circumference of the neck through the seventh cervical vertebra and the midthyroid region measured 33 cm. The transverse diameter was 13 cm, the right and left vertical vertebral were 5 cm each, the thickness, 2 cm.

The heart was not enlarged. There was simple tachycardia. The pulse rate was 104. The blood pressure was 120 systolic and 90 diastolic. The lungs were normal.

The abdomen showed an old appendectomy scar, otherwise it was normal.

Examination of the vagina showed a bilateral cervical laceration. The body of the uterus was normal. Results of the rectal examination were negative.

*Laboratory Data*—Results of roentgen examination of the chest were negative. Electrocardiographic tracings showed simple tachycardia. Examination of the blood revealed red blood cells, 3,750,000; hemoglobin, 75 per cent; white blood cells, 6,000; polymorphonuclears, 68 per cent; large lymphocytes, 2 per cent; small lymphocytes, 30 per cent. The urine was normal. The basal metabolic rate was plus 30 per cent.

The diagnosis was toxic adenoma of the thyroid of many years duration with marked mental manifestations recurring in attacks.

*Course Under Radium Treatment*—On March 31 and April 6, 1927 5,000 mg. hours of radium with the radium collar at 3 cm. distance were given to the thyroid region, and on April 19, 3,000 mg. hours with the block were applied to the thymus region. The result was extremely gratifying. Within one week after radium therapy was started, improvement in symptoms was noted. On May 3, 1927, only one month after the first application of radium was made, her only complaints were cough, slight expectoration and oppression in the chest. She felt strong. Her depression was gone. Her mood became hopeful and more cheerful. She began to gain in weight. Her pulse rate dropped to 72 per minute. The circumference of the neck had shrunk from 33 to 30.5 cm. (fig 7 B).

Reexamination fifteen months later, in July, 1928, showed the improvement persisting. Her weight had increased to 132 pounds (59.9 Kg.). Her pulse and basal metabolism were normal. During this entire period of observation her attacks of melancholia failed to recur (fig 7 C).

*Comment*—The most instructive features of this case were

1. The discovery of the adenoma at the early age of 6 years.
2. The development of toxic constitutional and local abdominal symptoms nine years after the appearance of the adenoma. The thyro-



Fig 7 (case 8) —*A*, toxic adenoma of the thyroid in a woman, aged 32. Toxic symptoms endured seventeen years, and were accompanied by marked mental manifestations recurring in attacks. The basal metabolism was plus 30. The circumference of the neck was 33 cm (March, 1927, before radium treatment). *B*, three weeks after radium treatment to the thyroid and thymus regions. There was marked improvement in constitutional symptoms, and a decided change in facial expression. The pulse rate was 72. There was a gain in weight, and a shrinkage of the circumference of the neck from 33 to 30.5 cm (May 10, 1927, after radium treatment). *C*, eleven months after a single course of radium treatments. The pulse and basal metabolism were normal. The patient gained 14 pounds (6.4 Kg) in weight. Mental symptoms did not recur, and shrinkage of the neck persisted (March, 1928, after radium treatment).

toxic condition was apparently overlooked. A local diagnosis of chronic appendicitis lead to appendectomy which failed to produce any relief. A low-grade smouldering toxic process continued with little, if any, increase in the size of the adenoma.

3 The added stimulus of pregnancy and the difficult adjustment of an irritable thyrotoxic patient to the trials, tribulations and frictions of marital life fanned the smouldering thyrotoxic flame into increased activity. The blunt of the intoxication predominantly affected the sensitive cells of the affective centers. The result was an outbreak of acute melancholia which did not subside for a year and a half. She had a spontaneous remission, but did not fully recover from her thyrotoxic condition. She remained nervous and irritable. She lost weight, and suffered from dyspnea and palpitation and had mild recurrent attacks of depression.

4 An acute influenzal infection aggravated all her thyrotoxic symptoms and was followed by distressing throat symptoms. Focal tonsillar infection was diagnosed. Tonsillectomy was performed but relief failed to follow.

5 Finally, after seventeen years of continuous thyrotoxic symptoms with attacks of melancholia and local phenomena of the throat, the patient received one application of radium to the thyroid and one to the thymus region, and relief from her thyrotoxic symptoms promptly ensued. A complete transformation occurred in her disposition. If one carefully examines figure 7, it will tell the accomplished result more eloquently than words can describe. It is clinical observations of this kind viewed by the light of radium therapy which force the unshakable conviction in one's mind that both in cases of classic exophthalmic goiter and in cases of toxic adenoma the brain and the rest of the nervous system and all the other systems in the body are only secondarily affected from a primarily diseased thyroid gland and not vice versa. Relief from thyrotoxic symptoms by local attack with radium on the thyroid speaks decidedly against the thyroid as a compensatory agent in either toxic adenoma or exophthalmic goiter. Boldly, in both conditions, it points unerringly to a diseased thyroid gland as the highly noxious destructive source from which toxic products emanate and flood the system and exert their most baneful and pernicious effects on all *loci minoris resistentiae*.

#### SUMMARY AND CONCLUSIONS

In his illuminating study of thyroid adenoma, one of the foremost American students<sup>87</sup> in health and disease of the thyroid gland

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<sup>87</sup> Marine D. Benign Epithelial Tumors of the Thyroid Gland. *J. M. Research* **22**, 229, 1912-1913.



stated "The term thyroid adenoma was formerly used by Rokitsansky,<sup>88</sup> Virchow,<sup>89</sup> and Wolfler<sup>90</sup> to include symmetrical hyperplasias of the whole gland. While at present there is a tendency to sharply distinguish morphologically between adenoma and diffuse overgrowth of the thyroid (goiter) and to criticize the earlier observers' use of the term 'adenoma,' nevertheless, the more extensive one's acquaintance with these growths becomes the more one is convinced that the point of the earlier writers was well taken, that there is no sharp division between benign epithelial tumors and diffuse overgrowths that some have been led to expect either anatomically or functionally."

In common with Marine<sup>87</sup> I fully endorse the views of the old masters in thyroid pathology and, therefore readily accept Aschoff's teachings that nodular goiter is synonymous with adenomatous goiter or adenoma of the thyroid, and that toxic nodular goiter is equally synonymous with toxic adenomatous goiter or toxic adenoma of the thyroid. Hence, clinically, a tentative diagnosis of toxic adenoma of the thyroid is warranted whenever a nodular goiter is associated with the constitutional symptoms of exophthalmic goiter with or without the ocular manifestations of the disease.

In recognizing toxic adenoma as a clinical-pathologic concept, I wish to stress strongly that neither clinically nor pathologically do I perceive any fundamental distinction between toxic adenoma and exophthalmic goiter except as the variation of a single disease. Nevertheless, for practical diagnostic and therapeutic reasons, the recognition of this variation is important, for in toxic adenoma the ocular signs are rarely present, the adenoma or adenomas may be small and readily disregarded if stress on this variation of thyrotoxicosis is omitted from the medical literature.

Eponymically, Parry's disease—and not Basedow's or Graves' disease—is the most appropriate designation for both toxic adenoma and exophthalmic goiter, for Parry was the first observer who described all varieties of toxic goiter.

Clinically, a nodular goiter without exophthalmos may be as toxic or even more toxic than a smooth, diffusely enlarged, or exophthalmic goiter with pronounced ocular signs. The prognosis in a severe case of toxic adenoma with myocardial insufficiency is much graver than that in a moderately severe case of classic exophthalmic goiter in which the patient has markedly bulging eyes and a fairly intact myocardium.

88 Rokitsansky, C. Zur Anatomie des Kropfes, Wien, 1849, cited by Marine.

89 Virchow, R. Die krankhaften Geschwulste, 1863, vol. 3, p. 15.

90 Wolfler, A. Ueber die Entwicklung und den Bau des Kropfes, Arch. f. klin. Chir. 29, 1, 1883.

Although toxic adenoma may run as severe a course as exophthalmic goiter, its clinical manifestations are usually milder, and the surgical results are more satisfactory than in classic exophthalmic goiter.

The more favorable surgical results in toxic adenoma are due not to any fundamental difference in nature from exophthalmic goiter but to a variation of a single disease. In exophthalmic goiter, generally the entire gland is diffusely involved in the pathologic process, while in toxic adenoma of the thyroid the gland shows one or several pathologic foci with intervening healthy tissue between the affected areas. Hence generally, the symptoms are milder, and surgical resection is more satisfactory than in exophthalmic goiter.

Surgical intervention, however, is no longer the only efficient means in the successful treatment of toxic adenoma of the thyroid. The same factors which are operative to make surgical intervention more successful in toxic adenoma than in exophthalmic goiter are equally operative in roentgen and radium therapy.

Of these two methods surgical intervention has been recognized until the present day by the majority of the medical profession as the method of choice, while roentgen and radium therapy have been slighted or rejected.

A review of the literature and my own observations fully justify the following conclusions:

Surgical intervention is no longer the only means of relief in dealing with toxic adenoma of the thyroid.

Radium therapy efficiently applied not only removes the thyrotoxic symptoms but also shrinks the tumor growth and thereby removes the compression phenomena of toxic adenoma of the thyroid.

Radium therapy, safe, efficient, free from surgical mortality, deserves first choice not only in dealing with exophthalmic goiter but also in the treatment of toxic adenoma of the thyroid.

Finally, it must not be forgotten, to obtain the best results in toxic adenoma as well as in exophthalmic goiter a combination of radium therapy plus rest in bed, proper diet and medication, is highly desirable.

# THE EFFECT OF THE PURINE BASE DIURETICS ON THE CORONARY FLOW \*

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CHICAGO

Reports based on experimental work concerning the effect of the salts of theobromine and caffeine, and later of theophylline, on the volume flow in the coronary arteries, began to appear shortly after the clinical report of Askanazy <sup>1</sup> in 1895. Taken as a whole, the collective evidence points definitely to a vasodilator action of these drugs on the coronary vessels. The work has been done almost entirely on preparations of the isolated heart, and with suspension preparations of arterial strips. While, for the most part, the results of such experiments can safely be taken as evidence of the actual pharmacologic effect of the drug clinically, there are certain objections. Especially is this true when there is a possibility that the action is a direct one on the vessel wall. In perfusion experiments a constant supply of the drug is reaching the tissues in a fixed dilution, permitting any amount to be taken up by the tissues in time. When a dose of the drug calculated to make the same dilution in the blood is injected into the circulation, one does not know how much is taken up by the tissues elsewhere, how quickly, or what the dilution is when it reaches the tissues to be tested, nor does one know what biochemical reaction in the blood may alter its action. In the isolated heart also, the vessel is free from the constant vasomotor changes present in the intact animal which might alter the response.

The only work on the intact animal available to us has been that of Sakai and Saneyoshi <sup>2</sup>. Their conclusion was that the vasodilator effects which they found may be ascribed to doses larger than those used clinically, and are referable to a rise in blood pressure.

For the past several years these drugs, and especially the salts of theobromine have been used in the Sunday morning clinic for patients with diseases of the heart at St. Luke's Hospital. The results are reported elsewhere by Gilbert and Kerr <sup>3</sup>. Some degree of relief from the anginal

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<sup>1</sup> From the Medical Department of Northwestern University

1 Askanazy. *Deutsches Arch f klin Med* **56** 209, 1895

2 Sakai and Saneyoshi. *Arch f d ges Physiol* **78** 331, 1915

3 Gilbert, N C, and Kerr, John Austin. *Clinical Results in Treatment of Angina Pectoris with the Purine-Base Diuretics*, *J A M A* **92** 201 (Jan 19) 1929

pain was obtained in more than half of the cases, and in a few cases the relief was almost complete. The unpleasant symptoms which sometimes accompany the use of these drugs was somewhat deterrent, this, however, could be obviated in most of the cases by a change in the preparations used and in the method of administration. The good results were obtained just when they would be expected—when there was the largest element of probable vasomotor spasm, and the least element of anatomic change in the vessels.

Because of what we considered good clinical results with the drugs, and because the previous experimental work could not be considered altogether conclusive it was determined to attempt further experimental work. The results are given briefly.

#### EXPERIMENTAL WORK

Direct measurement of the return flow in the coronary arteries in the intact animal must necessarily present many variables which are unknown. The operative procedures, the shock, and especially the traumatized thorax and open chest, are doubtless productive of changes in the basic conditions. Biochemical conditions in the blood may vary during the experiment with variations in the pulmonary ventilation, with the amount of saline introduced into the circulation and with other factors. But there is no variable which could be assumed to facilitate the action of vasodilator drugs.

Since the coronary flow is a direct function of blood pressure, and especially diastolic pressure, it would be demanded that this factor be controlled. The experiments recorded in this paper, with a few minor exceptions, resulted in a fall of both systolic and diastolic pressure, and rendered the control of this variable unnecessary. Variations of rate, as well as of other factors, such as venous inflow and tonus, have been shown by others to have no effect on the coronary flow when within ordinary limits (Anrep<sup>4</sup>).

In the experiments reported, dogs weighing about 6 Kg. were used. For the most part the Grehan anesthetic was used, a 5 per cent solution of chloroform in equal parts of alcohol and water. About 8 cc. per kilogram of body weight was administered through a stomach tube, preceded one-half hour by 0.01 cc. of morphine per kilogram of body weight. The dosage was varied slightly in proportion to the condition of the animal. On six dogs, chlorotone in dosages of from 0.25 to 0.30 cc. per kilogram was used. On two dogs, ether was used, and in one case paraldehyde.

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4 Anrep, G. V. *Physiol. Rev.* 6:596, 1926.

Blood pressure was recorded by means of a mercury manometer connected with the carotid. In a few cases a Hueithle apparatus was used, but this was discarded in favor of the mercury instrument.

The chest was opened to the right of the midline through the costal cartilages, and artificial ventilation was instituted. The cannula described by Morovitz<sup>5</sup> was slightly modified by introducing in the distal third enough of a curve so that when it was fixed in position in the coronary

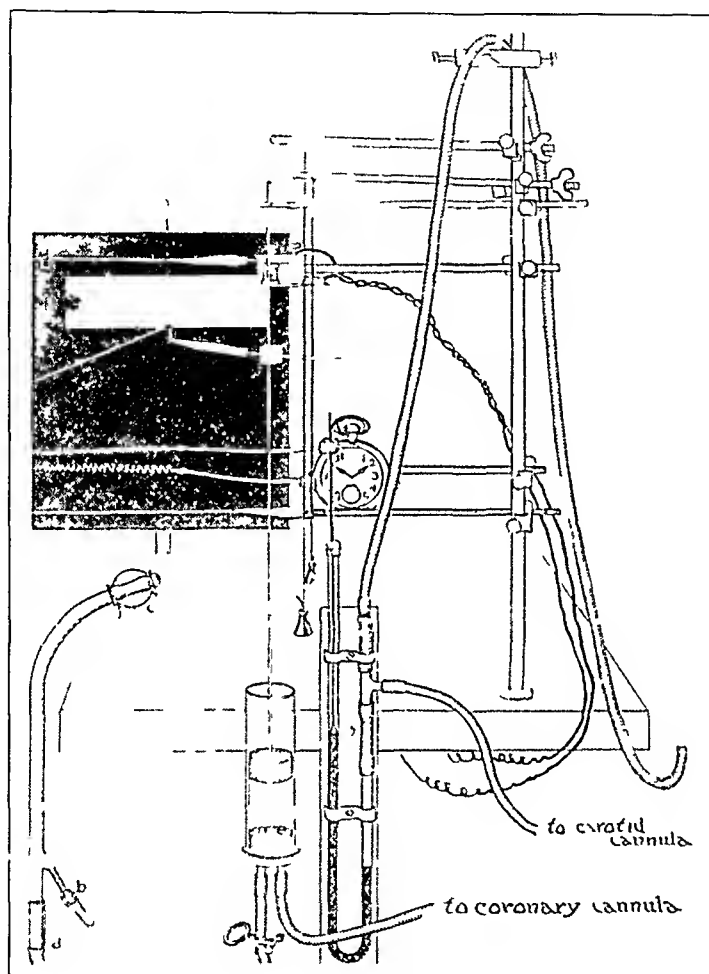


Fig 1—Apparatus for recording coronary flow and modified Morovitz cannula

sinus, the cannula would project out through the midline without exerting pressure on the heart or lungs, otherwise, it was used as described by Morovitz. The cannula was connected with the cylinder of a piston recorder, placed lower than the heart, and the rise of the fluid level in the cylinder was traced on a revolving drum. Slight changes in the rate of flow were shown by deviations from the straight gradient of ascent.

5 Morovitz and Zahn. *Deutsches Arch f klin Med* 116 366, 1914

The cylinder was emptied manually at intervals, and the blood returned through a warmed cylinder connected with the femoral vein. The height of the cylinder was adjusted so as to permit of a constant return flow. Small variations in return flow are shown at once by changes in blood pressure and consequent changes in the rate of coronary flow. No experiments are recorded in which the cannula was not firmly seated in the coronary sinus at autopsy. While the return flow from the coronary sinus measures approximately only about three fifths of the total coronary flow, and there are variations from this ratio, the ratio remains



Fig 2—Section of tracing, showing effect of the injection of 0.01 cc per kilogram of body weight of theobromine sodium acetate

constant for the individual animal in the experiment (Lovatt-Evans and Starling<sup>6</sup>)

The drug was introduced through the cannula in the femoral vein. When dilutions of the drug in the blood are given in the tables, the rate of injection was such as to permit of one or more circulatory cycles during injection, otherwise, the drug was injected rapidly. Control experiments with distilled water and tap water showed no effect on the coronary flow.

The doses used were average human doses corresponding to those suitable for a man weighing 75 Kg. In the case of administration of theophylline ethylenediamine, the 0.1 Gm ( $1\frac{1}{2}$  grains) tablets were used clinically with good results, and part of the experiments were based on this dosage. The ampules furnished contain 0.48 cc., and in part of the experiments the larger dosage was used.

In considering the results of the administration of any of the drugs here used, it is to be borne in mind that we do not know the state of dilatation when the drug is injected, as we do not know what factors are opposing further dilatation. Also, a vasodilator drug previously injected may influence the results obtained from the injection of other vasodilator drugs for an unknown period afterward. The effect of the second injection may be slight or absent because of an extreme dilatation.

TABLE 1—*Effects of Injections of Caffeine Sodium Benzoate*

Dog	Experiment	Anesthetic	Dose per Kg *	Dilution	Time of Injection	Effect			Per Cent Increase in Flow
						Blood Pressure		Pulse	
						Systolic	Diastolic		
52	2	Grehant	0.01	1:7700	35'	0	0	0	9.2
52	3	Grehant	0.01	1:7700	33'	-5.5	-4.5	+3	0
52	10	Grehant	0.01	1:7700	5'	0	0	-12	12.5
33	4	Grehant	0.0036			-15	-16	-9	0
53	2	Grehant	0.0033	1:9240	35'	+8	+6	-3	16.7
43	2	Grehant	0.0032			-18	-18	+9	15.4
42	1	Grehant	0.0071			-9	-9	+7	0
33	2	Grehant	0.0066			-4	-3	+12	0
41	1	Grehant	0.0066			-25	-24	+18	20
29	10	Grehant	0.0066						0
43	1	Grehant	0.0041			-16	-14	+18	8.3
49	1	Grehant	0.0032			-10.5	-11.5	+9	8.8

\* Dose, 0.0067 cc per kilogram, for a man weighing 75 Kg,  $7\frac{1}{2}$  grains (0.5 Gm.)

secured by the first injection.  $O_1$ , when small doses are used, an increased response may be elicited by subsequent doses when the concentration of the drug in the blood is increased. Because of this, only in the first experiment in each dog is there no possibility of influence by the previous injection of drugs.

The results obtained with injections of caffeine sodium benzoate are shown in table 1. The effect of this drug on the coronary flow was less than with any of the other preparations. In dog 42, there was no response in the first experiment with what would correspond to a full human dose. There was not, however, the fall in flow which might be anticipated from the fall in blood pressure. That there was not already a vasodilatation at the time of injection is shown by the fact that a rather large dose of euphyllin (0.007 cc per kilogram of body weight) gave an increase in flow of 100 per cent ten minutes later. In two cases there was an increase in flow with fractional doses in the first experiment. With the exception of one case (dog 53), the blood pressure fell. The pulse rate was accelerated in seven of the eleven cases.

Injectious of theocine sodium acetate (table 2) showed a more marked effect on the flow than was experienced when caffeine sodium benzoate was used. In dog 44, there was an increase of 30 per cent in the flow with one half of the estimated human equivalent. In two cases there was no response. In dog 29, approximately a full dose was given five minutes after a 58 per cent response had been obtained with theobromine sodium acetate. There was a decrease in coronary flow, as might be expected in the presence of a preexisting vasodilatation and a fall in pressure. In dog 45, there was also no increase in coronary flow. The experiment was made eighteen minutes after a 120 per cent increase in flow had been caused by another drug.

A fall in pressure and an increase in pulse rate was again observed in most of the experiments. The smaller doses in the last two experi-

TABLE 2—*Effects of Injections of Theocine Sodium Acetate*

Dog	Experiment	Anesthetic	Dose per Kg *	Effect			Per Cent Increase in Flow
				Blood Pressure		Pulse	
				Systolic	Diastolic		
45	6	Grehant	0 0038	— 4	0	+15	28 5
34	7	Grehant	0 0036	— 6	— 7	+ 6	34 5
39	2	Grehant	0 0035	— 8	—10	+20	28 5
44	2	Grehant	0 00336	— 7	— 5	+ 9	27 3
29	2	Grehant	0 0033†	— 6	— 8	— 3	—4 5
28	5	Grehant	0 0033	— 8	—10	+36	9 5
30	1	Grehant	0 0033	+10	+ 5	+ 3	21 4
26	5	Grehant	0 0033	0	0	0	3 3
45	4	Grehant	0 0019‡	—10	—10	+13	0
44	1	Grehant	0 0017	+ 2	+ 2	+ 6	30 7
39	1	Grehant	0 0016	+ 3	+ 5	+ 3	0

\* Dose, 0.0035 cc per kilogram, for a man weighing 75 Kg, 4 grains (0.26 Gm.)

† After large response with theobromine sodium acetate

‡ After extreme previous dilatation

ments did not cause a fall in pressure, but caused a rise, as did the almost full dose in dog 30.

The advantage of the vasodilator effect of the ethylenediamine in addition to that of the theophylline (theocine) is claimed for euphyllin (theophylline ethylenediamine). While we did not obtain as uniformly good results as those obtained by Guggenheimer and Sassa,<sup>7</sup> or Iwai and Sassa<sup>8</sup> in perfusion experiments on the empty beating heart, the effect was distinctly superior to that produced by theocine sodium acetate (table 3).

When there is as great a variability in results as must always obtain in work on the intact animal, it is possible that in a larger series of animals comparable results would have been obtained with the smaller

7 Guggenheimer and Sassa. *Verhandlungen der deutschen Gesellschaft für innere Medizin*, 35 Kongress, Wien, 1923, p. 101.

8 Iwai and Sassa. *Arch. f. exper. Path. u. Pharmacol.* 99: 215, 1923.



doses and greater dilution. As it was, experiment 1 in dog 63 showed a 25 per cent increase in flow with one half of the smallest human dose, and an estimated dilution in the blood of from 1 to 110,000.

The results obtained with theobromine and with its sodium acetate and sodium salicylate salts are shown in tables 4, 5 and 6. A greater

TABLE 3—*Effects of Injection of Euphyllin*

Dog	Experi- ment	Anesthetic	Dose per Kg *	Dilution	Time of Injec- tion	Effect			Per Cent Increase in Flow
						Blood Pressure		Pulse	
						Systolic	Diastolic		
56	2	Ether	0 008			-34	-30	+28	29 5
56	3	Ether	0 008			-13	-13	+36	40
43	4	Grehant	0 0077			-10	-10	0	18 75
42	2	Grehant	0 007			-14	-11	+ 2	100
48	6	Grehant	0 0058			- 7	- 7	-12	7 15
48	4	Grehant	0 0029			- 6	- 5	+18	37 5
58	3	Ether	0 0028			-18	-18	0	-12 5
59	5	Grehant	0 0023	1 26,813	16'	-12	- 9	+24	50
57	3	Grehant	0 002			- 6	- 6	+12	50
57	4	Grehant	0 002			- 6	- 6	+51	40
48	5	Grehant	0 0015			- 8	- 8	0	7 7
59	6	Grehant	0 0014	1 53,626	12'	- 8	- 7	+ 6	9 2
60	4	Grehant	0 00095	1 82,134	15'	+ 1	+ 1	0	9 5
60	3	Grehant	0 00076	1 102,667	8'	0	0	+ 9	0
60	2	Grehant	0 00038	1 205,334	15'	0	0	0	0
60	1	Grehant	0 00019			0	0	0	0
61	1	Grehant	0 0003			+ 4	+ 4	0	0
61	2	Grehant	0 0006			- 4	- 4	+18	0
61	3	Grehant	0 0006			- 2	- 2	0	0
61	6	Grehant	0 0012	1 64,167	6'	+ 2	+ 2	+ 3	20
61	7	Grehant	0 0012	1 64,167	13'	+ 2	+ 2	+ 3	25
63	1	Grehant	0 0007	1 110,367	8'	+ 6	+ 6	-15	25
63	2	Grehant	0 0014	1 55,188	17'	0	0	0	50

\* (Ampules) 0.0064 cc per kilogram, for a man weighing 75 Kg,  $7\frac{1}{2}$  grains (0.48 Gm.)  
(Tablets) 0.0013 cc per kilogram, for a man weighing 75 Kg,  $1\frac{1}{2}$  grains (0.1 Gm.)

TABLE 4—*Effects of Injection of Theobromine*

Dog	Experi- ment	Anesthetic	Dose per Kg *	Dilution	Time of Injec- tion	Effect			Per Cent Increase in Flow
						Blood Pressure		Pulse	
						Systolic	Diastolic		
57	2	Grehant	0 005	1 15,400	34'	+ 2	0	-12	33 5
58	1	Ether	0 00087	1 84,000	58'	-16	-16	- 3	78
58	6	Ether	0 00087	1 84,000	40'	+ 2	+ 2	0	5 25
63	3	Grehant	0 0012	1 66,220	32'	+ 2	+ 2	0	33
63	4	Grehant	0 00248	1 33,110	35'	- 4	- 4	+18	33
63	5	Grehant	0 005	1 16,555	47'	-10	0	+ 9	72 72

\* Dose, 0.005 cc per kilogram, for a man weighing 75 Kg, 6 grains (0.38 Gm.)

and more constant increase in the return flow through the coronary sinus resulted with the use of these drugs. This increase in flow was observed not only with the estimated dosage in every instance except when there was a previous extreme vasodilatation, but also with proportionate doses down to one eighth. Here again there was observed a decrease in systolic and diastolic blood pressure, with an increase in the pulse rate in most of the experiments. The exceptions were more frequent with the smaller doses.

TABLE 5—*Effects of Injection of Theobromine Sodium Salicylate*

Dog	Experiment	Anesthetic	Dose per Kg *	Dilution	Time of Injection	Effect			Per Cent Increase in Flow
						Blood Pressure		Pulse	
						Systolic	Diastolic		
17	7	Paraldehyde	0.035			0	0		16.7
14	4	Chloretone	0.03			0	0	+ 9	0
9	5	Chloretone	0.026			- 1	- 2	+ 6	15.4
12	3	Chloretone	0.024			- 8	- 4	+21	66.6
12	5	Chloretone	0.024			+ 4	+ 2	-12	37.75
12	11	Chloretone	0.024			6	- 2	- 6	25
12	12	Chloretone	0.024			+ 4		- 3	54.5
23	1	Grehant	0.0177			-25	- 8	- 6	50
23	5	Grehant	0.0177			- 8	- 2	- 9	83.7
17	1	Paraldehyde	0.0175			- 1	0	- 7	25
18	3	Grehant	0.0167			-14			33
20	6	Grehant	0.0166			- 4	- 2	+18	47
20	1	Grehant	0.0166			- 8	- 6	+27	32.2
15	1	Chloretone	0.0145			+ 2	- 2	+ 3	25
14	1	Chloretone	0.0135			0	0	0	0
14	2	Chloretone	0.0135			0	0	0	0
14	7	Chloretone	0.0135			0	0	+ 6	0
14	8	Chloretone	0.0135			0	0	0	0
9	2	Chloretone	0.013			- 1	- 1	+24	22
44	6	Grehant	0.01			- 4	- 4	+24	51.5
34	3	Grehant	0.011			-14	-10	- 3	13
27	1	Grehant	0.011			- 4	- 3	+ 3	40
35	3	Grehant	0.01			+ 4	- 7	- 3	37.5
35	4	Grehant	0.01			- 6	-14	+ 6	25
39	4	Grehant	0.01			- 6	0	+30	18.75
41	2	Grehant	0.01			-11	-12	+18	36.4
33	5	Grehant	0.01			- 7	-11	0	4.5
28	1	Grehant	0.01			-28	-23	+36	154.3
30	2	Grehant	0.01			-24	-23	+18	0
30	5	Grehant	0.01			-10	-10	+ 9	38.5
26	1	Grehant	0.01			- 4	- 3	+30	28.6
72	11	Grehant	0.01	1 7700	15'	0	0	+ 9	23.5
54	7	Grehant	0.01			0	+ 2	-12	15.4
55	2	Grehant	0.008			+20	+20	+ 3	60
56	1	Ether	0.005			+ 2	+ 4	0	29.5
54	2	Grehant	0.004	1 18,900	15'	0	0	0	50
58	2	Ether	0.0035			-12	-12	+ 9	27
53	1	Grehant	0.00125			+10	+10	+ 3	16.7
54	1	Grehant	0.00125			0	0	0	0

\* Dose, 0.01 cc per kilogram, for a man weighing 75 Kg, 11¼ grains (0.75 Gm.)

TABLE 6—*Effects of Injections of Theobromine Sodium Acetate*

Dog	Experiment	Anesthetic	Dose per Kg *	Dilution	Time of Injection	Effect			Per Cent Increase in Flow
						Blood Pressure		Pulse	
						Systolic	Diastolic		
9	10	Chloretone	0.0214			0	0	0	0
9	13	Chloretone	0.0214			0	0	0	Slight fall
29	1	Grehant	0.0103			- 8	- 4	0	58.4
38	1	Grehant	0.01					-18	52.9
36	2	Grehant	0.01			- 9	- 7	+12	123
40	5	Grehant	0.01			+12	+11	- 6	122.3
28	8	Grehant	0.01			-10	+ 2	- 6	29
52	5	Grehant	0.01	1 7700	22'	-11	-11	0	44.5
52	9	Grehant	0.01	1 7700	23'	- 6	- 6	0	25
54	3	Grehant	0.01			- 4	- 4	+ 9	22
54	6	Grehant	0.01			- 7	- 5	+ 3	4.5
41	5	Grehant	0.01			- 9	- 8	+ 6	137.8
33	8	Grehant	0.01			- 8	- 8	+ 9	0
30	9	Grehant	0.01			- 5	- 3	+24	31.25
47	4	Grehant	0.01			-14	-15	0	55.5
56	6	Ether	0.01	1 7700	20'	- 2	+ 2	+ 3	71.5
43	5	Grehant	0.0098			- 3	- 3	0	33.3
38	3	Grehant	0.0094			-11	-11	0	38.4
61	5	Grehant	0.006			+ 9	+ 5	0	57
36	1	Grehant	0.0047			- 1	+ 1	+14	26.6
51	2	Grehant	0.0042	1 18,287	56'	- 8	- 6	+12	25
61	9	Grehant	0.004	1 19,250	8'	+ 5	+ 2	0	100
51	1	Grehant	0.0021	1 36,000		- 6	- 6	+24	44
52	1	Grehant	0.00125			0	0	24	0
52	4	Grehant	0.00125			0	0	0	11.1
53	3	Grehant	0.00125			- 8	- 8	0	0

\* Dose, 0.01 cc per kilogram, for a man weighing 75 Kg, 11¼ grains (0.75 Gm.)

In two dogs there was no response in the first experiment with one eighth of the estimated dose, but dog 53 showed a 167 per cent increase of flow when given one eighth of the dose of theobromine sodium acetate, and dog 58 showed a 78 per cent increase when given one sixth of the estimated dosage of theobromine

In the cases in which no response occurred with more than one eighth of the estimated dosage, there was reason to assume a previous dilatation, as such instances occurred in other than the first injection, except when chloritone anesthesia was used. Because of failure in response or the smaller increase in flow with chloritone anesthesia, even when doses larger than normal were used, it was determined to investigate the effect of chloritone when injected intravenously. This is well shown in table 7. Similar results were obtained in two other experiments. It

TABLE 7—*Effect of Chloritone*

Experiment*	Drug	Dose per Kg	Effect			
			Blood Pressure		Pulse	Per Cent Increase in Flow
			Systolic	Diastolic		
1	Theobromine sodium salicylate	0.00125	0	0	0	0
2	Theobromine sodium salicylate	0.00125	0	0	0	50
3	Theobromine sodium acetate	0.01	—4	—4	+9	22.2
4	80 per cent alcohol	0.3 cc	—4	—4	—6	0
5	Chloritone in 2 cc of 80 per cent alcohol	0.027	After 120'	—16	—20	—57
			After 180'	—18	—20	—60
			After 240'	—12	—14	—60
6	Theobromine sodium acetate	0.01	After 5 min	—7	—5	+3
7	Theobromine sodium salicylate	0.01	After 11 min	0	+2	—12
						15.4

\* Dog no. 54 (7.4 Kg)

will be noted in the table that when one eighth of the estimated dose of theobromine sodium salicylate was given, there was no response, but when the same amount was added to that already in the circulation, five minutes later there was a 50 per cent increase in flow. Because chloritone was so much more readily soluble in alcohol, the effect of 0.3 cc per kilogram of 80 per cent alcohol injected slowly into the circulation was observed. There was a slight decrease in blood pressure and in pulse rate, but no change in the volume of the return flow through the coronary sinus. Chloritone, 0.027 cc per kilogram, dissolved in 80 per cent alcohol, was then injected into the circulation. This caused a marked decrease in blood pressure and in pulse rate, with a great increase in coronary flow. When a full dose of theobromine sodium acetate was given five minutes later, there was a decrease in the coronary flow, as would be anticipated with a further fall in pressure in the presence of an extreme dilatation. Sixteen minutes after the injection of chloritone,

the volume flow had decreased to a point where a full dose of theobromine sodium acetate was able to elicit a slight response

A similar check with chloroform (0.0058 cc per kilogram) in dogs under ether anesthesia showed respectively in three experiments no change in flow, an increase of 3.7 per cent and an increase of 29.4 per cent

The effect of sodium salicylate and sodium acetate was investigated in order to determine their influence on the action of the corresponding theobromine salts. Sodium acetate in three experiments in doses of 0.01 cc per kilogram gave no result in one case, and an increase in the coronary flow of 37.5 per cent and 26.6 per cent in the two other cases. Sodium acetate in doses of 0.01 cc per kilogram in three experiments gave increases of 120, 47 and 83.5 per cent in the coronary flow, and in a dose of 0.0076 cc per kilogram, an increase in flow of 89 per cent. It is to be observed, however, that the double salts of theobromine in the experiments cited showed no advantage over theobromine when used in corresponding dosage.

The elapsed time between the administration of the drug and the effect on the coronary flow decreased with increased dosage and increased concentration in the blood. With fractional doses, a considerably longer time was necessary before a maximal effect occurred.

#### SUMMARY

It will be observed that the results recorded in this paper are similar to those obtained in perfusion experiments on the isolated heart, and especially those reported by Heathcote<sup>9</sup>. The order in point of efficacy are theobromine and its salts, theophylline ethylenediamine, theophylline sodium acetate and caffeine. A vasodilator effect on the coronary arteries, as shown by an increased return flow through the coronary sinus, is shown with doses corresponding to the average human doses, and fractions of such doses.

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<sup>9</sup> Heathcote, R. St. A. *J. Pharmacol. & Exper. Therap.* **16** 327, 1920

# UNDULANT FEVER PRESENTING THE CLINICAL SYNDROME OF INTERMITTENT HYDRARTHROSIS \*

B M BAKER, JR, MD

BALTIMORE

Malta fever is gradually assuming a prominent rôle among the infectious diseases of this country. In 1906, Craig<sup>1</sup> reported the first case of Malta fever contracted in the United States from a natural source and not through laboratory infection. From 1905 to 1924 several reports of similar cases appeared in the American literature (Yount and Looney,<sup>2</sup> Gentry and Ferenbaugh,<sup>3</sup> Lake<sup>4</sup> and others). Although there may be some doubt about the source of infection in the case described by Craig,<sup>1</sup> the infection in the subsequent cases could with considerable certainty be traced to goat's milk.

Although *Bacillus abortus* of Bang had been recognized as a cause of abortion in cattle for many years, and infection by the organism was known to be widespread among cattle in many countries, including the United States, it was not until the work of Shaw<sup>5</sup> and the later investigations of Evans<sup>6</sup> that it became evident that *Bacillus abortus* and *Brucella melitensis* were organisms which are almost indistinguishable by cultural, morphologic and serologic examination. In a continuation of her work, Evans<sup>7</sup> has included under the broad term *Brucella melitensis* strains from human, porcine, caprine and equine sources.

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1 Craig. The Symptomatology and Diagnosis of Malta Fever, with the Report of Additional Cases, *Internat Clin* **4** 89, 1906

2 Yount and Looney. Malta Fever, with a Preliminary Report on Cases Occurring in Arizona, *Arizona M J* **1** 18, 1913

3 Gentry, Ernest R, and Ferenbaugh, Thomas L. Endemic Malta Fever in Texas, *J A M A* **57** 1045 (Sept 23) 1911

4 Lake. Malta Fever in Southwestern United States, *Pub Health Rep* **37** 2895 (Nov 24) 1922

5 Shaw. Mediterranean Fever Reports, London, parts 4, 1905-1907, vol 16

6 Evans, A C. Further Studies on Bacterium Abortus and Related Bacteria, *J Infect Dis* **22** 576, 1918

7 Evans, A C. Serological Classification of *Brucella Melitensis* from Human, Bovine, Caprine, Porcine and Equine Sources, *Pub Health Rep* **38** 1948 (Aug 24) 1923

The first infection in man proved to be due to *Brucella melitensis*, variety abortus, was reported by Keefe,<sup>8</sup> in 1924. Keefe's study suggested that infection by *Bacillus abortus* might occur in man through the use of milk<sup>9</sup> or milk products obtained from infected cows and under such circumstances might produce in man a disease similar to Malta fever. Since the publication of Keefe's paper, instances of infection by *Bacillus abortus* have been reported from all parts of the country. In the reported cases, emphasis is usually laid on the fact that the goat could be excluded as a source of infection or that the infection was probably derived from cow's milk. During the past year three cases of undulant fever have been observed in the Johns Hopkins Hospital. The diagnosis was confirmed by recovery of *Brucella melitensis* from the blood stream in all three instances.

Hardy<sup>10</sup> has studied the prevalence of the disease in Iowa, basing the diagnosis on positive agglutination tests and has found it to be probably as common as typhoid fever and paratyphoid fever combined. Abortus infection has recently been reported from Canada (Scozzafave and Warner<sup>11</sup>), and Kristensen<sup>12</sup> has collected 150 cases in Denmark.

Sir David Bruce<sup>13</sup> defined Malta fever as "A disease of long duration characterized clinically by continued fever, profuse perspiration, constipation, frequent relapses, rheumatoid or neuralgic pains, swelling of the joints or orchitis." The pains in the joints are considered characteristic, and in many cases are a distressing feature, necessitating at times a differential diagnosis from acute rheumatic fever. Shaw<sup>14</sup> reported a case in which the patient had swollen, painful joints. In the cases of Gilman and Kennedy,<sup>15</sup> there was suppuration of the costosternal and costochondral articulations, and *Brucella melitensis* was recovered in pure culture from the pus. One patient of

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8 Keefe, C. S. Report of a Case of Malta Fever Originating in Baltimore, Maryland, Bull. Johns Hopkins Hosp. **35** 6, 1924.

9 More detailed history of Keefe's case brings out the fact that the patient, in the course of his duties as laboratory technician in the department of histology, collected fresh material from hogs at a slaughter house. From the study of the patient's strain Dr. Theobald Smith concluded that the infection was probably of porcine origin.

10 Hardy. Malta Fever, Pub. Health Rep. **43** 503 (March 2) 1928.

11 Scozzafave and Warner. Brucella Abortus Infection in Man, Canad. M. A. J. **19** 177, 1928.

12 Kristensen, M. Undulant Fever in Denmark, Ugeskr. f. Læger **90** 869, 1928.

13 Bruce. Undulant Fever, in Osler. Modern Medicine, ed. 3, 1920, vol. 1, p. 634.

14 Shaw. Undulant Fever in America, Science **67** 217 (Feb. 24) 1928.

15 Kennedy. Notes on a Case of Chronic Synovitis, or Bursitis, Due to the Organism of Mediterranean Fever, J. Roy. Army M. Corps **2** 178, 1904.

Watkins and Lake,<sup>16</sup> after apparent recovery from undulant fever, was left with "chronic lumbago"

The excellent clinical descriptions of undulant fever by Keefer,<sup>8</sup> Kiistensen,<sup>12</sup> Grigni and Savorini,<sup>17</sup> Kern,<sup>18</sup> Hardy<sup>19</sup> and others portray the disease and its bizarre manifestations in considerable detail, and no attempt will be made in this communication to review this phase of the subject at length. It is desired, however, to direct attention to one manifestation of undulant fever which hitherto has not been described in relation to this disease. Although it is possible that certain instances of intermittent hydatidiosis may have been, in fact, caused by *Brucella melitensis*, an actual association between the clinical syndrome of intermittent hydatidiosis and undulant fever has not before been recognized.

#### REPORT OF CASE

*History*—G. J., aged 47, an electrician, living in Virginia, entered the Johns Hopkins Hospital on Nov. 3, 1927, complaining of swelling of the knees.

The family history revealed the fact that his father had died at the age of 74 of heart trouble, and his mother at the age of 70 of cancer of the stomach. No member of his family had ever suffered with diseases of the joints.

The past history showed that he had measles, chickenpox and mumps. Seventeen years ago, at the age of 30, he was ill for six weeks with fever that was termed "typho-malaria," as it was unaffected by quinine. The fever was intermittent in type, with remissions in the morning and rises in temperature as high as 103 F. in the evenings. Anorexia, general arthralgia, malaise, loss of weight and profuse sweating accompanied the fever. While recovery was slow, it was considered complete. Previous to the onset of this illness he was working on a farm in Virginia and had been engaged in slaughtering hogs.

The patient had never married. His habits were exemplary.

*Present Illness*—He considered himself in excellent health until the onset of his present illness, which he dated definitely to the last week in March, 1927, when on a cold, wet evening, he stood on a street corner conversing with a friend for an hour or more. On arising the following morning he was aware of a soreness in the tendons behind both knees "as if they had been exercised too much." So far as he knew there had been no undue physical strain. When he walked his knees were stiff, both knees being equally affected. After two days of this discomfort the right knee began to swell and continued to do so for approximately three days, and then the swelling subsided as suddenly as it had risen. For about a day the left knee felt normal, but to his surprise when the swelling in the right knee was at its height, the left knee enlarged also and followed precisely the course taken by the right. During the period of enlargement the knees were stiff, but there was no local redness or heat, and locomotion was not seriously embarrassed.

16 Watkins, N. W., and Lake, G. C. Malta Fever with Especial Reference to Phoenix, Ariz., Epidemic of 1922, *J. A. M. A.* **89** 1581 (Nov. 5) 1927.

17 Grigni and Savorini. Clinical and Epidemiologic Symptoms of Undulant Fever, *Gior. di clin. med.* **9** 359, 1928.

18 Kern, R. A. Clinical Aspects of *Brucella melitensis*, Variety *Abortus*. Infection in Man, *Am. J. M. Sc.* **176** 405, 1928.

19 Hardy, A. D. The Epidemiology of Undulant (Malta) Fever in Iowa, *Pub. Health Rep.* **43** 2459 (Sept. 21) 1928.

The patient said that this sequence of events, running in cycles of seven days each, continued with great regularity from the onset of his trouble to the day of admission to the hospital. The only change that he noted was a slow but steady increase in stiffness with consequent difficulty in walking. By August, 1927, he had to give up his work. He entered a local hospital, where a "glassful" of fluid was removed from each knee several times without any effect on the well established periodic swelling.

With the onset of the swellings in the joints the patient began to feel generally run down, though never sufficiently so to go to bed. His appetite was poor, and he experienced an almost constant dull headache. Occasionally he felt chilly and then hot, so that he thought he had fever. There were no sweats. He lost 23 pounds of weight (10.4 Kg) in six months.

*Physical Examination*—Examination of the patient revealed a temperature of 99 F, pulse rate, 100, respirations, 22, blood pressure 120 systolic and 75 diastolic, height, 166.3 cm, weight, 117 pounds (53.1 Kg).

The mucous membranes were pale, and there was a slight, yellowish pallor of the skin. He had evidently lost weight. The gait was abnormal, obviously due to inability to flex properly the right knee. There were no cutaneous hemorrhages or hemorrhages in the ocular fundi. The tonsils were not enlarged, but there was moderate reddening of the right anterior tonsillar pillar. Several enlarged glands were felt in the anterior and posterior triangles on both sides of the neck. The epitrochlear glands were not felt. The thyroid gland was not enlarged. The lungs were clear to percussion and auscultation. The heart was not enlarged, and the sounds were loud and clear. No thickening of the radial or brachial arteries was noted. The liver and spleen were not felt, nor did they seem enlarged to percussion. The prostate gland was small and firm.

Examination of the muscles showed them to be of good tone and bulk. There were no disturbances in the recognition of all sensory stimuli. All the tendon reflexes were equal and active on the two sides.

The skeletal system was normal with the exception of the right knee joint. It was much larger than the left. There was no redness, discoloration, increased temperature or edema of the overlying skin. Definite ballottement of the right patellar was demonstrated together with a considerable accumulation of fluid in the quadriceps pouches and obliteration of the normal bony markings of the knee joint. There was definite crepitation when the joint was moved, and passive flexion beyond 90 degrees caused considerable pain. The left knee presented no apparent abnormality.

*Laboratory Examination*—The blood count showed red blood cells, 4,070,000, hemoglobin, 83 per cent, white blood cells, 9,440, polymorphonuclear neutrophils, 71 per cent, polymorphonuclear eosinophils, 1 per cent, lymphocytes, 22 per cent, mononuclears, 6 per cent. Examination of the smear revealed no abnormality. The urine on admission had a specific gravity of 1.025, no sugar, albumin, 1 plus. Microscopic examination of the urine showed a rare hyaline cast and many white blood cells and epithelial cells. After several days on a high fluid intake the urine became normal and remained so throughout the patient's sojourn in the hospital.

The Wassermann reaction was negative. Phenolsulphonphthalein excretion was 60 per cent in two hours. The tuberculin test (0.1 mg) intracutaneously was negative. The basal metabolic rate was +6. No hypersensitivity to epidermal extracts, dairy products, grains, fish, vegetables or fruits was found by intracutaneous tests. X-ray pictures of the knees revealed a slight degree of infectious arthritis (fig 1). The other larger joints were normal on roentgen examination.

Figures 2 and 3 show the appearance of the knees at a time when the swelling was maximal in one and minimal in the other.





Fig 1—Roentgenogram of the knees showing a slight degree of infectious arthritis



Fig 2—Appearance of the knees at a time when the swelling was maximal in one and minimal in the other



Fig 3—Appearance of the knees at a time when the swelling was maximal in one and minimal in the other

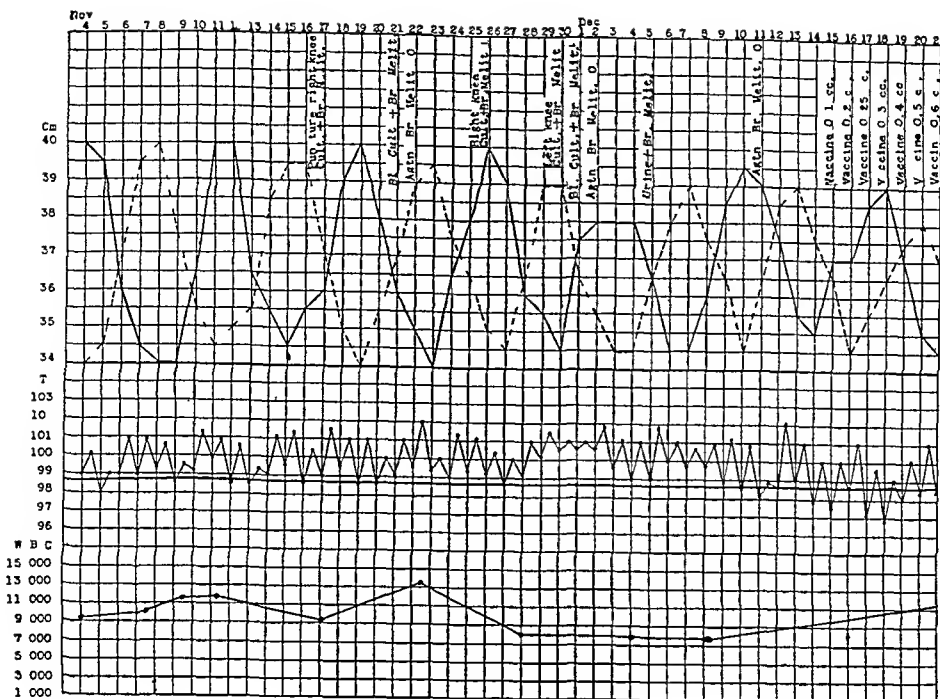


Fig 4—The curves represent the fluctuations in the size of the knee joints, variations in temperature and the white cell count. The patient weighed 117 pounds (53.1 Kg). The red blood cells numbered 4,000,000, the hemoglobin content was 83 per cent, the polymorphonuclear neutrophils, 71 per cent, the eosinophils, 1 per cent, and the mononuclears, 28 per cent.

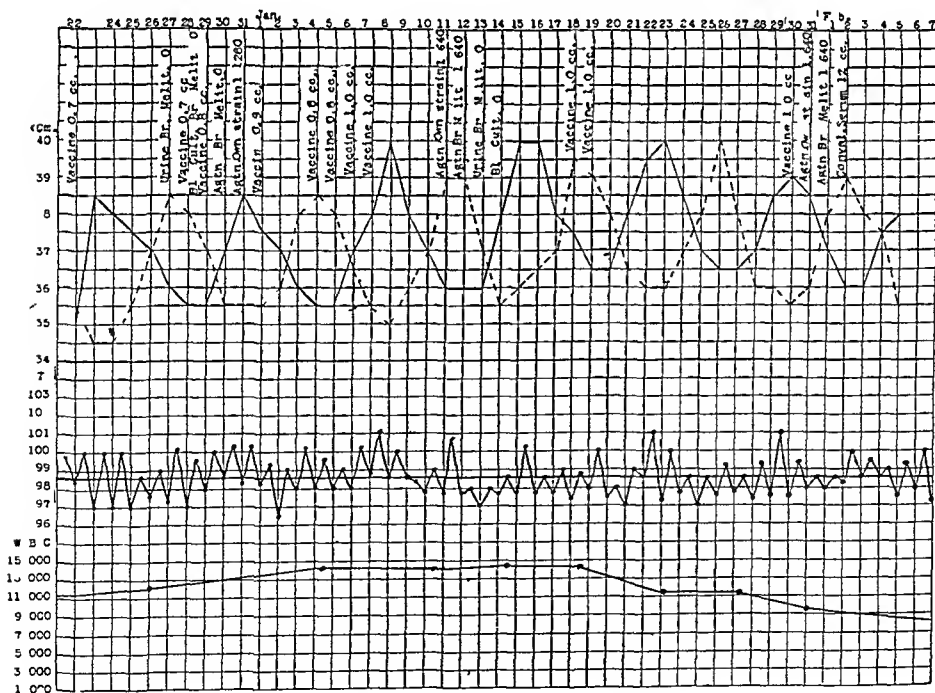


Fig 5—The curves represent the fluctuations in the size of the knee joints, variations in the temperature and the white cell count. The patient weighed 124 pounds (56.2 Kg). The red blood cells numbered 4,000,000.

*Course of Illness*—Both knee joints were measured daily at the same hour, and reference to figures 4 and 5 confirms the patient's story of an extraordinary regularity in the swelling. It can be seen from the charts that for weeks without interruption, between Saturday evening and Sunday evening, the swelling in the right knee reached a maximum. The left knee followed a similar schedule, approximately three and a half days after the right.

In the charts the highest and lowest temperatures for the day and the leukocyte counts are plotted. The occurrence of persistent fever associated with slight leukocytosis suggested a search for some infection.

Accordingly on November 17, the right knee was punctured, and 30 cc of a thick, brownish yellow fluid, clotting quickly, was withdrawn. The white blood cells of the fluid numbered 5,200 per cubic centimeter, 75 per cent were lymphocytes, and 25 per cent polymorphonuclear leukocytes. A small quantity of a similar fluid was again withdrawn from the right knee on November 26, and from the left knee on November 30.

Direct smears from these fluids stained by the method of Gram, contained a moderate number of tiny gram-negative bacilli frequently occurring in pairs. The fluid was cultured on the occasion of each tapping. On November 22, and again on November 30, cultures were made from the blood stream. On November 5, 5 cc of urine was injected into the groin of a guinea-pig. From each assay an organism was recovered which proved on further study to belong to the *Brucella melitensis* group.

On November 22, the patient's serum failed to agglutinate organisms of hygienic laboratory strains of *Brucella melitensis* 426, 428 and 456. Again on November 30, there was no agglutination, using these strains as well as the organisms recovered from the patient's own knee joints. A third attempt to demonstrate agglutinins in the patient's serum on December 11 failed.

*Treatment*—A solution of potassium arsenite, sodium cacodylate and quinine in appropriate doses had no effect on the fever, swelling of the knees or the patient's symptoms. Because of the fact that it was impossible to demonstrate agglutinins in the patient's serum for *Brucella melitensis*, administration of an autogenous vaccine was begun on December 15. He received 13 cc of vaccine between Dec 15, 1927, and Jan 30, 1928, prepared from organisms recovered from his knee joints and blood stream.

On February 2, he was given intramuscularly 12 cc of serum from a patient (A S reported by Keefer) who had recovered from Malta fever and whose serum contained agglutinins for the patient's organism. On February 11 an additional 8 cc was given, and this dose was repeated on February 19.

*Further Course*—Prior to the administration of vaccine the clinical picture had not changed, the patient had not gained weight, the fever had persisted, and the knees had continued to swell as they had done on admission. Thirteen days after administration of the vaccine was started, the patient's serum, in a dilution of 1:640, agglutinated the organisms recovered from his knees and blood stream, fourteen days later his serum, in a dilution of 1:640, agglutinated known strains of *Brucella melitensis*. Almost immediately after commencement of the use of the vaccine, the temperature began to approach normal. His appetite improved, and he felt generally stronger. He felt that the stiffness in his knees accompanying the peaks of swelling was less noticeable. Reference to figure 6 will show the effect on the hydrarthrosis.

Following the administration of convalescent serum, the improvement was striking. The temperature became normal and remained so. He felt well and gained weight rapidly. The leukocytosis disappeared, the hemoglobin percentage

rose to 90, and the red blood count to 5,000,000. Two blood cultures made on Dec 28, 1927, and on Jan 14, 1928, remained sterile for twenty days, and cultures from the urine were negative for *Brucella melitensis*. The stiffness and pain largely disappeared from the knees, and while the base line of measurement of the joints became elevated, the fluctuations in the size of the joints diminished greatly. He was discharged on Feb 24, 1928.

Unfortunately he was forced to return immediately to work, which necessitated standing for from six to eight hours daily. The knees began to swell again, but caused him little, if any, discomfort.

The patient was last heard from on Sept 15, 1928. He had been constantly at work since leaving the hospital, but the periodic swelling of his knees had slowly returned. For two days each week the pain and stiffness were marked, but the

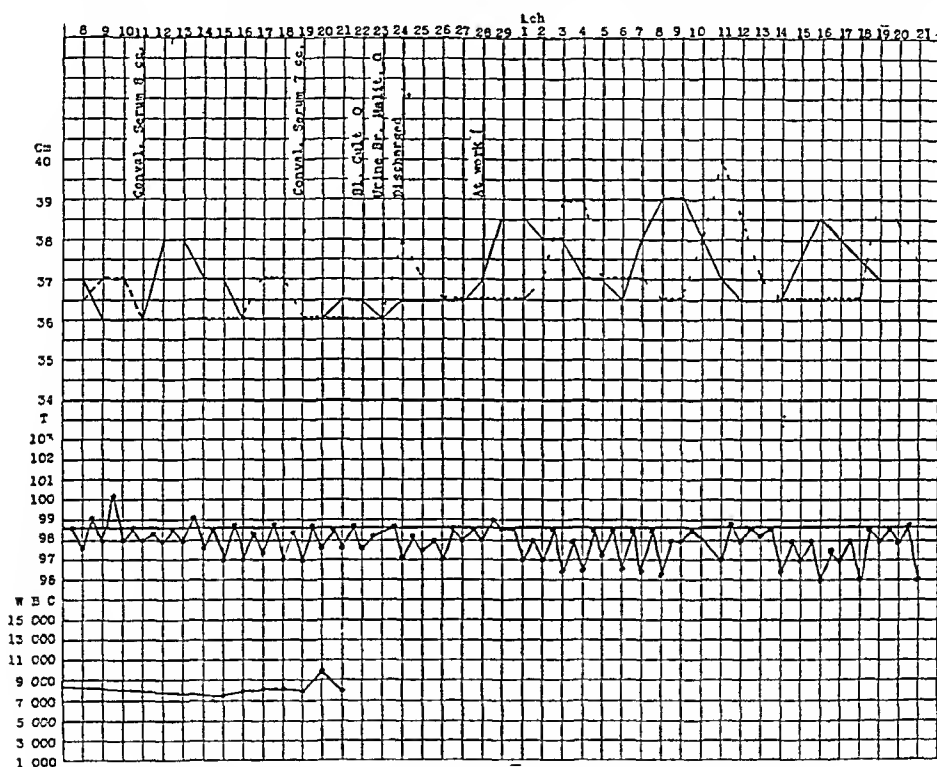


Fig 6—The curves represent the fluctuations in the size of the knee joints, variation in the temperature and the white cell count. The patient weighed 131 pounds (59.4 Kg). The red blood cells numbered 5,000,000, the hemoglobin content was 90 per cent, the polymorphonuclear neutrophils, 57 per cent, the eosinophils and basophils, 5 per cent, and the mononuclears, 38 per cent.

remainder of the week he passed in moderate comfort. Otherwise, he had remained well, none of the symptoms associated with his general infection had returned and estimations of the temperature in the morning and evening, daily since discharge, showed that he had remained afebrile.

#### BACTERIOLOGIC OBSERVATIONS

*Cultures from Joint Fluids*—Approximately 1 cc of fluid was allowed to flow freely over the surface of slants of beef infusion agar of  $p_H$  7.4 at the bedside immediately after aspiration. The tubes were

incubated at 37.5 C, and no culture was pronounced sterile until it had been incubated for twenty days. The first signs of growth occurred on the sixth, seventh and eighth days, in cultures made on three separate occasions.

*Blood Cultures*—Two methods were used. In the first, 8 cc of blood was laked with 80 cc of sterile distilled water and centrifugated at high speed for fifteen minutes. The supernatant fluid was discarded, and the sediment mixed with 45 cc of dextrose agar of  $p_H$  7.4 and 8 cc of sterile ascitic fluid and poured into several Noguchi tubes. These were stoppered with cotton swabs and allowed to incubate at 37.5 C for twenty days before being discarded.

*Results of Agglutination Tests Made with Normal Serum, the Patient's Serum and the Patient's Organisms Against the Patient's Serum, Brucella Melitensis and the Serum of One Known to Have Malta Fever*

	1 10	1 20	1 40	1 80	1 160	1 320	1 640	1 1280	1 2560	1 5120
Normal serum vs patient's organisms										
	No agglutination									
Normal serum vs known <i>Brucella melitensis</i>										
	No agglutination									
Patient's serum vs patient's organisms										
11/30/27	0	0	0	0	0	0	0	0	0	0
12/11/27	0	0	0	0	0	0	0	0	0	0
12/28/27	0	0	0	0	+	+	+	0	0	0
1/11/28	0	0	0	0	+	+	+	0	0	0
1/30/28	0	0	0	+	+	+	+	0	0	0
2/ 2/28	0	0	0	+	+	+	+	0	0	0
Patient's serum vs known <i>Brucella melitensis</i>										
11/22/27	0	0	0	0	0	0	0	0	0	0
12/11/27	0	0	0	0	0	0	0	0	0	0
12/28/27	0	0	0	0	0	0	0	0	0	0
1/11/28	0	0	0	+	+	+	+	0	0	0
1/30/28	0	0	0	+	+	+	+	0	0	0
2/ 2/28	0	0	0	+	+	+	+	0	0	0
Patient's organism vs serum from a patient known to have Malta fever	0	0	0	+	+	+	+	0	0	0

Controls of suspensions of the organisms in each test were negative.

The second method consisted of inoculating each of five flasks containing 80 cc of beef infusion broth  $p_H$  7.4 with 2 cc of the patient's blood and incubating for twenty days before pronouncing them sterile. The organism was recovered by the use of both methods.

*Identification*—The organism grew luxuriantly on beef infusion agar. Grayish, opaque, moist, rounded colonies, from 2 to 5 mm in diameter, first appeared on the sixth day after inoculation. The organisms were nonmotile and did not retain Gram's stain. Both bacillary and coccoid forms occurred in the cultures, but the bacillary forms predominated in young cultures. Organisms frequently occurred in pairs, but longer chains were seldom seen. There was no fermentation in maltose, levulose, mannite, saccharose, raffinose or dulcitol.

*Agglutination Reactions*—Macroscopic agglutination tests of the patient's serum in dilutions from 1 10 to 1 5120 at 56 C for two hours were made with organisms from fluid from the patient's knee joints and from the blood, as well as with three organisms of the *Brucella melitensis* group obtained from the hygienic laboratory<sup>20</sup> Normal human serum and saline controls were set up in each test The results are given in the accompanying table

The proagglutinoid zones were present in all tests Cooling the serums for forty-eight hours in the icebox, heating them undiluted for an hour at 56 C, or allowing them to stand undiluted at room temperature for several weeks had no effect on the appearance of the proagglutinoid zone Allowing the racks of tubes to stand at room temperature for seventy-two hours after they had been read caused a disappearance of the proagglutinoid zone No explanation is given for this observation

*Animal Inoculation*—The patient's strain was sent to Dr Theobald Smith for study The lesion produced by inoculation into guinea-pigs simulated closely, but not absolutely identically, that produced by bovine *Bacillus abortus*

#### COMMENT

There is no doubt that this patient had undulant fever The recovery of *Brucella melitensis* from the blood stream, the presence of agglutinins in the serum of high titer, together with the clinical course, make the diagnosis undeniable

Joint symptoms commonly form part of the picture of undulant fever, and occasionally are pronounced In this case the joint symptoms were singularly striking The effusions into both knee joints appeared and disappeared with clocklike regularity every seven days, and this remarkable course of events continued for months without interruption When the patient was first seen, a diagnosis of intermittent hydrarthrosis was made In an effort to determine the etiologic factor of this obscure malady, it was discovered that the patient had Malta fever and that *Brucella melitensis* existed in large numbers in the synovial effusions

Hydrops intermittens articulorum has been known and regarded as one of the curiosities of medicine since 1845 Perrin<sup>21</sup> first described the condition and cited as accompaniments of the hydrarthrosis slight fever, aching joints, headache and anorexia, all of which were present in the clinical picture of the case reported here

<sup>20</sup> These strains were sent by Dr Alice C Evans

<sup>21</sup> Perrin Cas curieux de contracture partielle intermittente, Union med 25 821, 1878

In 1864, Moore<sup>22</sup> reported the second case and three years later added another<sup>23</sup> Eighty-three instances of the disorder are now to be found in the literature The one feature common to all cases is the periodic hydarthrosis, the time intervals separating attacks varying from several days to several weeks

Garrod<sup>24</sup> and Benda<sup>25</sup> have written excellent descriptions of the disorder Diagnosis rarely offers any difficulty, for intelligent patients can prophesy with great accuracy not only the day but often the hour at which an attack will commence Age, sex and social status apparently have no bearing on the patients who present this rare picture Blanc<sup>26</sup> reported an instance in which mother and daughter were victims of intermittent hydarthrosis In the great majority of cases the condition involves one or both knee joints, which were believed to have been perfectly healthy previous to the onset of hydarthrosis In certain instances, patients give a history of antecedent arthritis or trauma

There has been no uniformity of opinion regarding the etiology of this peculiar disease Senator<sup>27</sup> reported two cases and concluded from a review of the literature that the etiology was not the same in all cases in some instances the periodic effusions depending on abnormalities in the vasomotor system, and in others on inflammatory changes in the affected joints

Because of the frequent preceding history of ague (Perin,<sup>21</sup> Moore,<sup>22</sup> Marsh<sup>28</sup> and others), the view was long held that malarial fever might be responsible for the periodicity of intermittent hydarthrosis The discovery by Ross of the short and constant life cycles of the malarial parasites necessitated the abandonment of this conception Many, but not all cases, are associated with high fever, in others, an enlarged spleen has been observed In Bierring's<sup>29</sup> case, the patient

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22 Moore Periodical Inflammation of Knee Joint, *Lancet* **1** 485, 1864

23 Moore Two Cases of Periodical Inflammation of the Right Knee Joint, *Tr Medico-Chir Soc Edinburgh* **1** 21, 1867

24 Garrod Concerning Intermittent Hydarthrosis, *Quart J Med* **3** 207, 1909-1910

25 Benda Intermittirende Gelenkwassersucht, *Allg med Centr-Ztg* **69** 471, 483, 495, 507 and 521, 1900

26 Blanc Observation d'hydarthrose intermittente héréditaire, *Loire med* **17** 287, 1898

27 Senator Ueber intermittirende Gelenkwassersucht, *Charite-Ann* **21** 224, 1896

28 Marsh An Affection of the Knee Possibly Due to Malaria, *Tr Clin Soc London* **38** 147, 1905

29 Bierring, W L Intermittent Hydarthrosis, *J A M A* **77** 785 (Sept 3) 1921



noted a regularity of the swelling of his knee joint following an illness described as typhoid fever

There have been a number of efforts to demonstrate organisms in the fluid aspirated from affected joints. In all attempts, heretofore, so far as one is aware, the fluids have shown no growth on culture. Hartmann,<sup>30</sup> in the joint fluid from a typical case, observed a "typhoid-like bacillus" but was unable to cultivate it. Pulawski<sup>31</sup> noted a "*Diplococcus*" in direct smears from the synovial fluid but could not identify it.

These facts suggest the possibility that other cases presenting the clinical syndrome of intermittent hydrarthrosis might prove, on careful bacteriologic examination, to be instances of infection by a member of the *Bacillus abortus* group. It might be argued that in the majority of the reported cases of hydrops intermittens articuloium there are no signs or symptoms of a chronic infection. This is likewise true at present, of the patient in the case reported, for whereas he has regularly recurring effusions into the knee joints he is afebrile and asymptomatic, and it is further well recognized that mild symptoms of undulant fever frequently pass unheeded by the patient.

It is hoped that this report will stimulate careful bacteriologic study of cases of intermittent hydrarthrosis and systematic observations of the joints in cases of Malta fever.

#### SUMMARY

1 A case of infection by *Bacillus abortus* arising in Virginia is reported.

2 In addition to many of the features of undulant fever the patient presented a periodic swelling of the knee joints, diagnosed intermittent hydrarthrosis.

3 Organisms of the *Brucella melitensis* group were isolated repeatedly from the blood stream and from fluid from the knee joints.

4 Specific agglutinins appeared in the blood after the administration of an autogenous vaccine.

5 Definite disappearance of the signs and symptoms of the infectious disease followed the administration of *Brucella melitensis* vaccine and serum from a patient who had recovered from undulant fever.

6 There was amelioration of the subjective joint disturbances and a temporary alteration in the hydrarthrosis following this treatment.

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30 Hartmann. Ueber einen Fall von Spondylitis deformans mit intermittierendem Hydrops der Gelenke, Inaug. Diss., Königsberg, 1889.

31 Pulawski. Ein Fall von periodischer Gelenksschwellung, Wien klin. Wchnschr. **27** 421, 1914.

7 It is concluded that in this case the intermittent hydrarthrosis was part of the general picture of infection from *Brucella melitensis*, and it is suggested that infection by a member of this group of organisms might prove to be the cause of the clinical syndrome, intermittent hydrarthrosis, in other patients

8 It should be emphasized that during the period in which *Brucella melitensis* was cultured from the blood and urine, there were no agglutinins in the patient's serum. Thus differential diagnosis cannot be based solely on agglutination reactions

# THE PATHOLOGIC ASPECT OF SOME EPILEPSIES\*

ALFRED GORDON, M D

PHILADELPHIA

The literature contains numerous examples of material lesions in the cerebrum which are associated with typical epileptic convulsions of the jacksonian or general type. Among the latest pathologic records may be mentioned tumors of the pontocerebellar angle, the angular gyrus, the temporal convolutions and the pituitary gland, dilatation of the lateral ventricles, hemorrhage in the occipital lobe, and thrombophlebitis of the under surface of the frontal lobe<sup>1</sup>. It is evident that a pathologic process in many portions of the brain may be accompanied by epileptic seizures, and these areas may therefore be considered as epileptogenous zones. In the present contribution a pathologic lesion in a rather rare localization of the brain is described, the lesion, during the patient's life, was a stimulating surface for convulsive discharges. In the absence of clinical evidences of gross pathologic involvement of the brain, particularly in cases of focal epilepsy, it is well to refer to the possibilities of invasion of the ventricles and especially of the lateral ventricles.

Ventricular walls are covered by ependymal lining membranes consisting of columnar and ciliated epithelium. In the ventricular cavity in a state of suspension lie the choroid plexuses with their villi, which are constantly brought into contact with the ependyma of the ventricular walls. Should the latter be in a state of inflammation or otherwise abnormally disturbed, there would be sufficient cause for the villous processes of the choroid plexuses to produce an irritation in the brain and, through the process of diffusion of the stimulus to the cortex along association or commissural fibers, to lead to reactions such as epileptic convulsions. Two examples are presented incriminating the ventricular cavities of the brain as the direct cause of epileptic convulsions during the patient's illness. In one, the ventricular ependyma alone was found to be diseased, in the other, the choroid plexuses were chiefly affected. No other lesion was found in either of the brains. As I am concerned in this paper chiefly with the pathologic aspect of the problem, the details of the clinical pictures of the cases will be omitted.

The patient in the first case was a middle-aged colored man, who presented frequent convulsive attacks (with loss of consciousness) confined to the left arm, with turning of the head to the left side. There were also ataxia, involvement of the deep sensibilities in the left

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\* Submitted for publication, Jan 26 1929

1 Gordon, A. J. Nerv & Ment Dis 61 142, 1925

aim, and finally left-sided hemianopia. A right-sided lesion was suspected in the brain. A decompressive operation was declined by the patient's relatives. The patient died during one of these attacks.

At autopsy all the abdominal and thoracic viscera were found to be normal. After being hardened, the brain presented on transverse anteroposterior section most uncommon observations, which were confined exclusively to the anterior cornua of the lateral ventricles. The lesion was pronounced in the right horn, and only slightly evident in the left horn. There was an unusually large quantity of fluid in both cornua. The ependyma had lost its uniform smoothness and was covered by numberless miliary nodules. Histologically, the latter presented cells of partly necrotic material, some of them were under the ependyma, some had destroyed it and some were in its surface. Their relative size was not equal, some of them being larger and longer than others, some were close to the surface and formed thick branches at a certain distance from the surface. They consisted of crowded round cells which followed the branches of the original nodules. Many vessels in this vicinity had mononuclear cells similar to those of the nodules. Some blood vessels were thrombotic and greatly dilated, and had thickened walls. In the latter, the inner layer was shiveled and torn in some places. The ependyma itself immediately beneath the miliary nodules was much thickened and covered thickly between the nodules by round cells. In some areas there was solution of continuity of the ependyma, which solution continued deep in the subependymal tissue. The inner walls of the separated portion were covered with round cells. As to the nature of the ependymal nodules, it is difficult to say. They did not have the histologic composition of tubercles. It would seem reasonable to call them miliary gummas. This view is substantiated, I think, by the fact that many vessels in the vicinity had mononuclear cells in their walls.

In the second case the patient was a boy, aged 10, who had had epileptic seizures since the age of 5. They were all of a generalized character and typical in their individual manifestations. There were no somatic symptoms deserving special mention.<sup>2</sup> The patient died from an intercurrent bronchopneumonia.

At autopsy all thoracic and abdominal viscera were found to be intact. A systematic study of the brain was made both macroscopically and microscopically. Special emphasis was laid on the histologic state of the cortex, in addition to a detailed examination of all tracts, fibers and nuclei. The only pathologic tissue that could be determined was found in the choroid plexuses, and in the ependyma of the anterior horn of the lateral ventricles. Externally, the plexuses appeared to be

<sup>2</sup> Gordon, A. J. *Nerv & Ment Dis* 67:445, 1928

greatly congested, and were thick, large, and hard under the fingers. The histologic study of the sections was made after the usual process of hardening. The staining was done with ammonia-carbim. The numerous glomeruli, which are held together by the delicate connective tissue stroma and which present a villous-like appearance, were seen with their cubic epithelial cells and their main constituents, namely blood vessels. The latter were filled with thrombi of all sizes, and some of them were surrounded by a thickened external wall as the result of an inflammatory process evidently of long standing (fig 1)

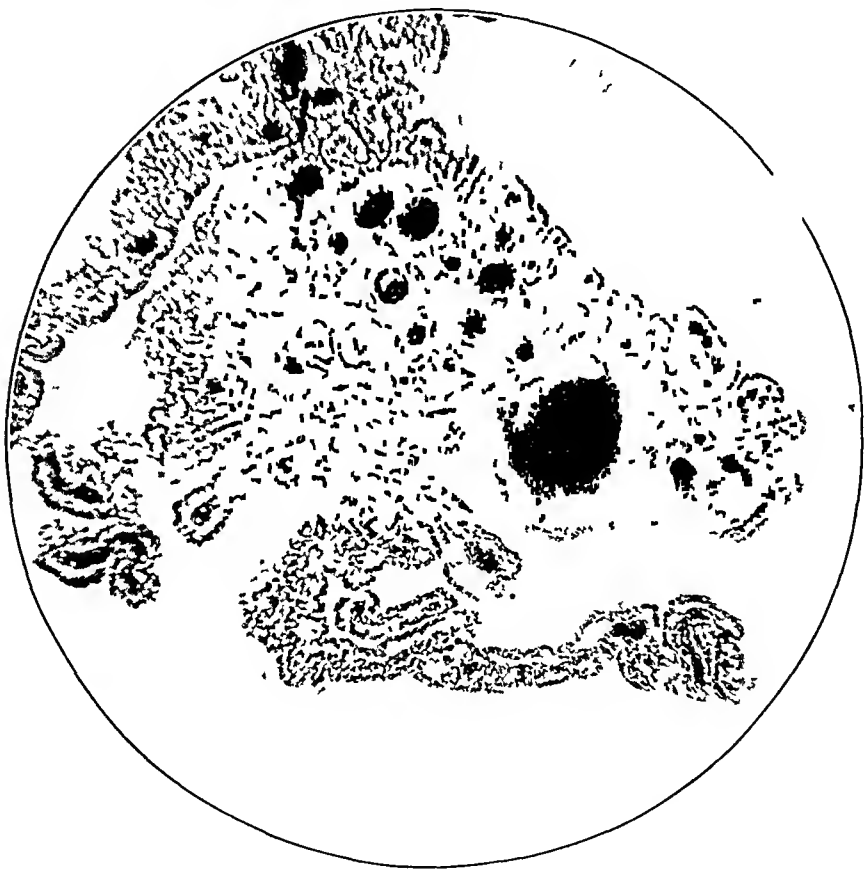


Fig 1—Choroid plexus. The blood vessels are filled with thrombi and surrounded by thickened external walls.

One finds in this instance, therefore, an original inflammation of the choroid plexus followed by hemorrhages within them. Since the choroid plexuses are practically a convoluted mass of highly vascular processes of the pia which covers the walls of the ventricles, sections of the latter were examined microscopically. They were found to be thickened and similar to the plexuses. Their blood vessels were also filled with thrombi but not to the same extent (fig 2). The entire pathologic process was therefore continuous from one to the other, with this difference, however, that the hemorrhage was less pronounced in

the membrane of the ventricular walls than in the plexuses. The disorder consequently lies in the pia mater of the lateral ventricles. The other ventricles of the brain were normal in appearance and on histologic studies.

#### COMMENT

To sum up, in the two cases described in this paper the pathologic process is confined to the lateral ventricles of the brain and to their contents, thus demonstrating that in addition to the other organic

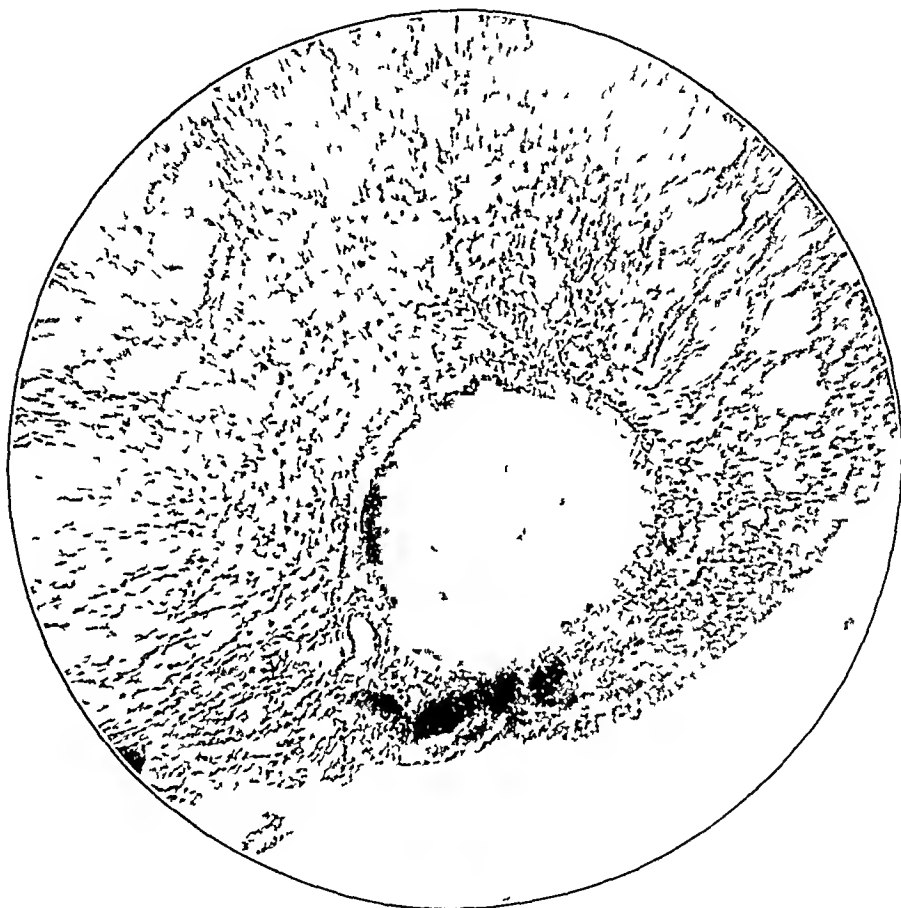


Fig 2—Choroid plexus. The pia of the walls of the ventricles is thickened. The blood vessels are filled with thrombi.

localizations of epilepsy in the cerebrum the ventricular cavities may play the same rôle of an epileptogenous zone. Ferrier, in his "Functions of the Brain," referred to his experimental investigations on the ventricular walls, which on electrical stimulation produced spasmodic muscular contractions. Ferrier's observations had been corroborated by experiments of Coirville and Duret.

The pathologic observations of the two cases are not a common occurrence. Ventricular foci have been rarely reported in connection with epilepsy. Not only the lining of the ventricular walls of the

choroid plexuses, but a pathologic state of the physical properties of the cerebrospinal fluid in the ventricles may play an important part in cerebral irritation resulting in convulsive seizures. In a recent contribution<sup>3</sup> a case of hydrocephalus was described in which frequent epileptic attacks were caused by increased tension of that fluid in the lateral ventricles. A withdrawal of a certain amount of that fluid from the lateral ventricles was followed by freedom from seizures during nine months.

The particular interest of the present contribution lies in the observations on the patient in the second case who during life presented manifestations of the common form of so-called idiopathic epilepsy in which an underlying organic lesion is ordinarily not expected. Besides the interesting histologic observations, the cases are instructive from the standpoint of localizations. Apparently, functional disorders may have an organic basis in areas other than those which are classically established. The present contribution adds a new rare document to those already existing which concern a vast variety of pathologic foci found in organic epilepsy. It warrants being placed on record on account of the unusual localization and the peculiar character of the lesions. It might also have been of interest to consider the mechanism of epileptic convulsions in cases of involvement of the ventricular walls and of the ependyma with the choroid plexuses. One might also have been interested in considering the association, commissural and projection pathways extending from the stimulated or irritated surface to the motor cells of the cortex, which, in the last analysis, are the province of the discharge of motor power resulting in convulsive seizures. Finally, it might have been of interest to be reminded of the experimental work done in that direction. But the object of the present contribution is not to show the physiologic or the clinical aspect of the problem of so-called functional or organic cases of epilepsy, but to present exclusively a pathologic document of an uncommon involvement of the contents of cerebral ventricles to the exclusion of any other lesion in the brain.

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3 Gordon, A. Hydrocephalus with Cessation of Persistent Epileptic Convulsion after Puncture of the Lateral Ventricles, *J A M A* **88** 1234 (April 16) 1927.

# MOTILITY OF THE RECTUM IN NORMAL AND IN CONSTIPATED SUBJECTS \*

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AND

A C IVY, M D

CHICAGO

Operative experiments on laboratory animals and roentgen studies on man have yielded most of the knowledge concerning the muscular activity of the colon. The information obtained with the roentgen rays is limited because only gross changes are revealed. Operative experiments on animals also have some shortcomings due to inability to elicit subjective symptoms or to the abnormal conditions which anesthesia and surgical intervention represent.

This is a study of the movements of the rectum before and after a meal and further shows the symptoms produced by the prolonged presence of a mass in the rectum. A balloon inserted into the lower colon of man through a proctoscope and filled with water has served as a medium for recording movements of the colon. Although the lower bowel was emptied of fecal matter before the experiment started, the results are interpreted as applying to a filled colon because the size and shape of the balloon are not unlike a formed fecal mass.

## METHODS

Twenty-one medical students who had healthy bowel action and twelve patients from the clinic who were constipated and users of cathartics were the subjects. All experiments were started shortly after the subject had defecated normally or as the result of an enema. All records were made while the subject was lying on his right side. A toy balloon measuring about 12 by 2.5 cm, tightly fastened to rubber tubing, was well greased with petrolatum and inserted into the lower sigmoid and rectum through a proctoscope. Long tissue forceps were used to hold the balloon in place while the proctoscope was being withdrawn, 150 cc of water warmed to 38 C was forced into the balloon. The pressure was measured with a mercury manometer (in about half of the experiments). Then the tubing from the balloon was connected with a water manometer placed on a shelf about 5 feet (1.5 meters) above the level of the subject. Tracings were made on a slowly moving drum for periods of at least thirty minutes before and after the subject ate. Sixteen subjects carried the balloon all day (from six to twelve hours) and were instructed to note especially the occurrence of symptoms such as headache, malaise or mental haziness.

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\* From the Departments of Physiology and Internal Medicine of Northwestern University Medical School



## RESULTS

The intracolonic pressure in millimeters of mercury was measured in ten normal and four constipated subjects. As shown in the tables, the pressure varied from 11 to 21 mm. The average was between 17 and 20 mm. (Ten of the fourteen readings were in this range). There

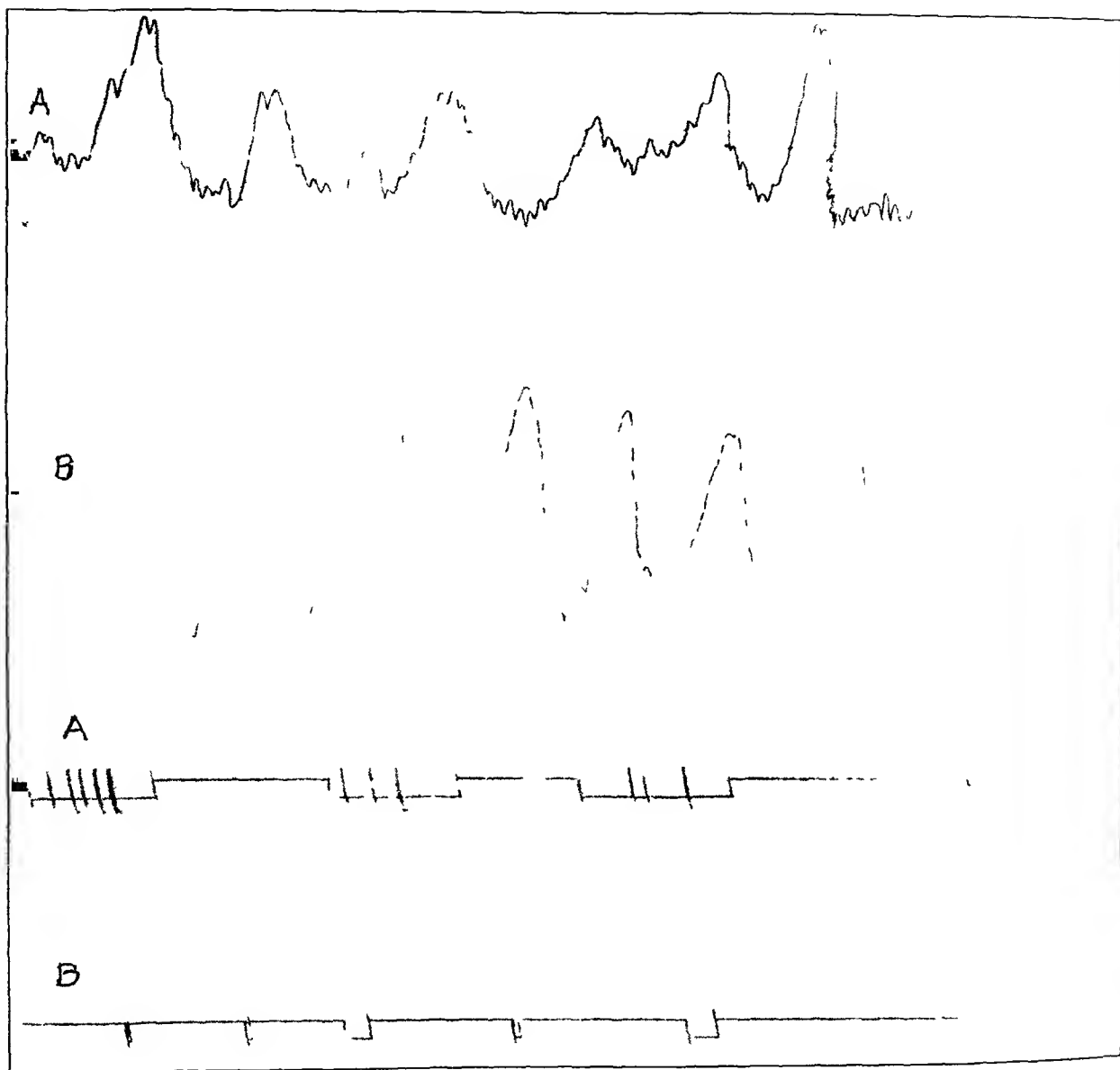


Fig 1 (subject C R)—Steep contractions which occurred before and after eating in normal subject. *A* indicates before a meal and *B*, after a meal.

was no appreciable difference in the pressure of the two groups (constipated and normal).

The sensation produced after the balloon was filled with water varied as to degree, but in all there was an immediate sensation of fullness accompanied by a desire to defecate. Usually, after a few



Fig 2 (subject E W) —Tonus rhythm which occurs before and after eating in constipated subject No steep contractions occurred *A* indicates before a meal and *B*, after a meal

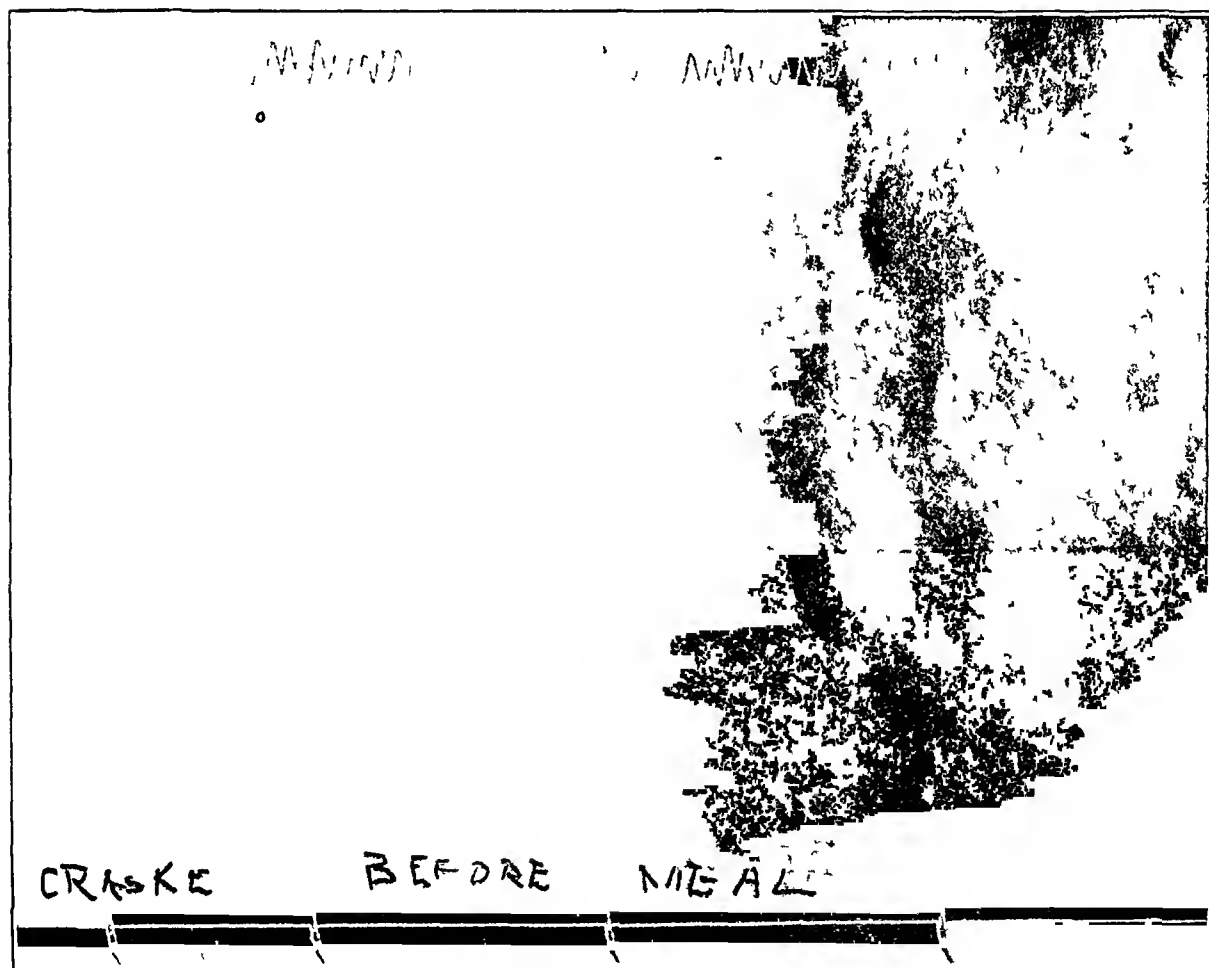


Fig 3—Record of normal subject showing only tonus rhythm before a meal

minutes, the sensation lessened or disappeared. However, in all of the normal group painful "urges" developed. These painful sensations lasted only a few seconds and generally became more frequent and severe as time went on. The most painful sensations were experienced by the sixteen who carried the balloon all day. The pain of one was so severe that he was unable to retain the balloon more than two hours. A signal magnet was used to record painful sensations while tracings were being made.

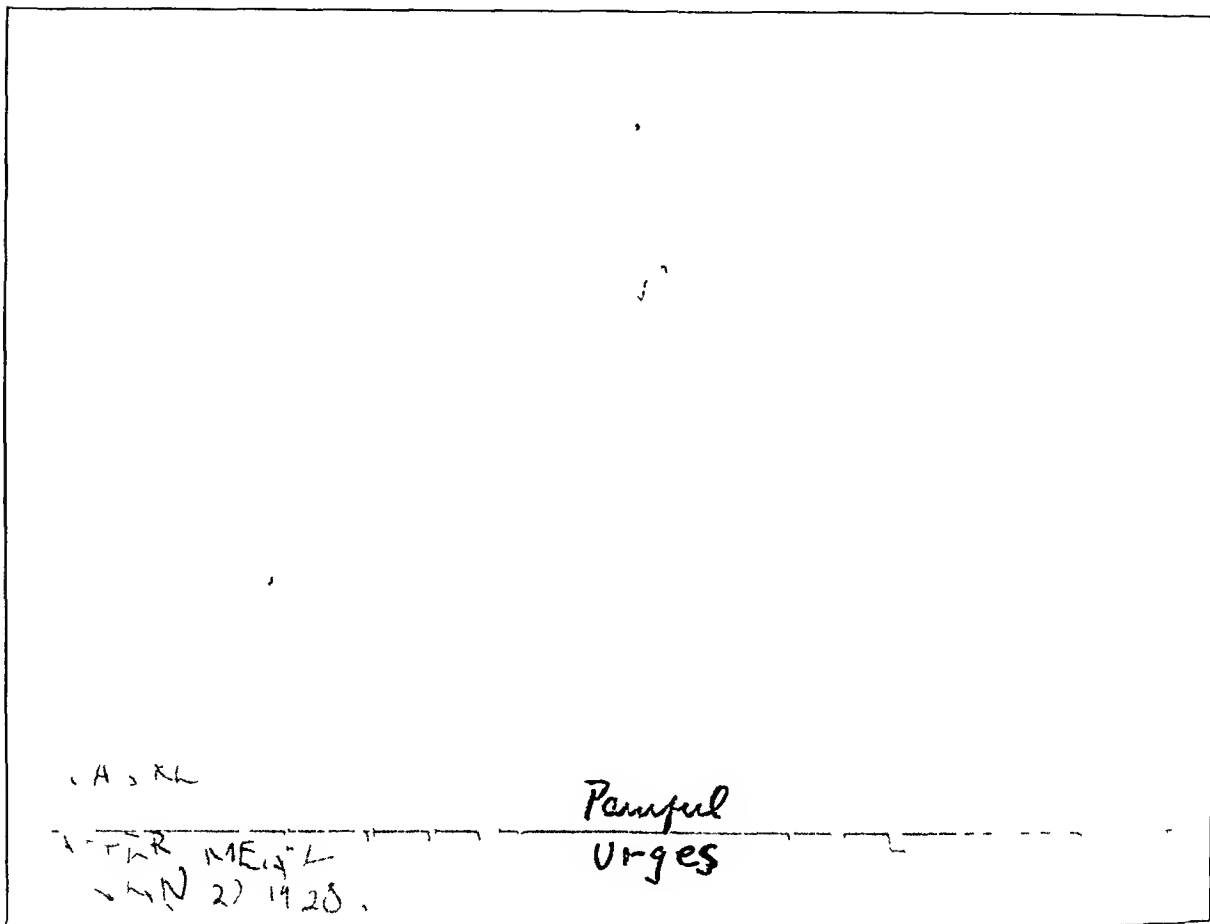


Fig 4—Record of same subject shown in figure 3, showing steep contractions after eating

After the balloon had been in place several hours, all subjects complained of a tight sensation in the hamstring group of muscles which some described as an ache. One complained of pain along the course of the left sciatic nerve. After the removal of the balloon, many had the sensation of "walking on air."

No symptom characteristic of the autointoxication syndrome was produced, even in those who carried the balloon for long periods.

The tracings show two types of contractions slow, slight, rhythmic elevations (a tonus rhythm) and steep contractions. A tonus rhythm was present in all of the normal group and in ten out of twelve of the constipated group. The steep contractions were present in all of the normal group but in only four of the constipated group. In five, steep contractions occurred only after meals. The painful urge was

TABLE 1—*Summary of Tracings in Group with Normal Bowel Action*

Subject	Painful Urge	Tonus Rhythm	Steep Contractions	Painful Urge	Tonus Rhythm	Steep Contractions	Pressure in Mm of Hg
T V	Slight	+	0	Moderate	+	++	
F A	0	+	0	0	+	+ ?	
M E	0	+	0	Marked	+	++	
L E	Moderate	+	++	Marked	+	++	
G U	Marked	+	++++	Marked	+	++++	
C R	Marked	+	++++	Marked	+	++++	
B V	0	+	+	0	+	+	
W A	Slight	+	++	Slight	+	+++	16
S I	0	+	+++	0	+	++	
B El	0	+	+	Moderate	+	+	17
S A	No determination			Moderate	+	+++	
C H	No determination			Marked	+	+ ?	18
P O	Slight	+	+++	Slight	+	+++	22
H O	0	+	+	Marked	+	++++	17
H L	Marked	+	+++	Moderate	+	++	21
L A	Marked	+	++++	Marked	+	+++	18
A D	Marked	+	++++	Marked	+	++++	18
C R	Slight	+	++	Marked	+	+++	
C A	0	+	++	Slight	+	++	15
C An	Slight	+	0	Moderate	+	+	19
B Chr	0	+	++	Slight	+	++	18

TABLE 2—*Summary of Tracings in Group Who Were Constipated*

Subject	Painful Urge	Tonus Rhythm	Steep Contractions	Painful Urge	Tonus Rhythm	Steep Contractions	Pressure in Mm of Hg
E W	0	+	0	0	+	0	
J N	0	+	0	0	+	0	
J D	0	+	0	0	+	+	
J N	0	+	0	0	+	+	
C G	0	+	0	0	+	0	
C F	0	+	0	0	+	0	
N S	Slight	+	0	Slight	+	+	
C P	0	+	0	0	+	+ ?	
M B	0	0	0	0	0	0	18
E M	0	0	0	0	0	0	18
V C	0	+	0	0	+	0	11
K H	0	+	0	0	+	0	12

always associated with a steep contraction wave and was usually synchronous with it. Many of the steeper waves, however, were not accompanied by painful sensations.

## COMMENT

Welch and Plant<sup>1</sup> have recently studied the activity of the colon in dogs by inserting balloons filled with water into the colon through permanent fistulas. They have demonstrated irregularly recurring

<sup>1</sup> Welch, P. B., and Plant, O. H. A Graphic Study of the Muscular Activity of the Colon, *Am J M Sc* **172** 261 (Aug.) 1926

changes of tonus usually with superimposed contractions and in three experiments on human beings have shown similar activity in the lower colon. They demonstrated increased muscular activity after eating when the colon was full and refer to this as a feeding reflex. Our experiments on a larger series of human beings have confirmed the presence of two types of activity in the normal colon, and this is interpreted as applying to a filled colon because the balloon is the equivalent of a fecal mass.

Comparative studies on constipated and normal subjects have shown that steep contractions and a synchronous painful urge are infrequent in the constipated group. This seems to indicate that the threshold for sensation in the constipated man is raised. It also seems likely that the steep contraction is one of the involuntary aids to the act of defecation and occurs infrequently in those who are constipated.

In five experiments, the steep contraction did not occur until food had been taken. This might be taken as evidence of a gastrocolic reflex. In the constipated group neither painful urges nor increased activity was demonstrated after eating.

Alvarez<sup>2</sup> expressed the belief that the symptoms of so-called auto-intoxication, such as headache, malaise, dopiness and mental haziness which commonly are present in constipated people, are due to the mechanical distention of the lower colon by the fecal mass. He produced such symptoms by stuffing the rectum with cotton. Our studies do not support his contention.

#### SUMMARY

Tonus rhythm and steep contractions are normal movements of the filled lower colon of man.

A balloon shaped like a fecal mass in the lower colon of man produces symptoms described as a painful urge but does not produce symptoms like those ascribed to auto-intoxication.

Painful urges are synchronous with steep contractions. In some experiments there is increased activity after eating (gastro-colic reflex).

Patients who are constipated and have the habit of taking cathartics do not complain of painful sensations while the balloon is in the colon and have infrequent steep contractions.

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2 Alvarez, W. C. Intestinal Auto-intoxication, *Physiol. Rev.* 4: 352, 1924.

## Book Reviews

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THE CLIMACTERIC (THE CRITICAL AGE) By GREGORIO MARANON, Professor of Medical Pathology in the Madrid General Hospital, Member of the Royal National Academy of Medicine Translated by K S Stevens Edited by Carey Culbertson, M D Price, \$6.50 Pp 425, including index and 18 illustrations St Louis C V Mosby Company, 1929

The first five chapters deal with the alleged pluriglandular factors in the menopause symptoms the ovarian factors, the thyroid factors, the hypophysial factors and the suprarenal factors There is a chapter on the vegetative nervous system during the menopause There are eleven chapters describing the symptoms in relation to the menopause, and in addition three chapters dealing with the psychic symptoms In these chapters the author touches on nearly every variety of disease that may occur during the menopause There is one chapter on the climacteric of the male and two chapters on the therapy of climacteric symptoms in the female

Dr Maranon is a facile and prolific writer in the field of the endocrines Unfortunately, he is not a critical one He tells one in the preface that "all the theory in the book is based on the present knowledge of the internal secretions much of which does not go beyond mere hypotheses Yet we have profited by them in our work" This profiting by endocrine hypotheses appears in accepting practically all of them as proved facts, and on that basis building up a hypothetic diagnosis and therapy Almost any disease known to man may, of course, appear as an incident during the period of the menopause Because of the frequency of nervousness and neurocirculatory disturbances in the menopause, Maranon concludes that there is a condition of hyperthyroidism and hypersuprarenalemia nearly always present In fact, one is told categorically that "independent of the size of the thyroid gland castration creates, if not actually active hyperthyroidism, at least a hyperthyroid predisposition" Part of the menopause symptoms are said to be due to an excess secretion of epinephrine In addition, the author puts great emphasis on "constitution or temperament" in the etiology of the disorders of the climacteric The ease with which the author obtains evidence for his views may be indicated by a few examples

"Let us consider the differences between the inhabitants of northern and southern Spain Those of the northern are of vigorous athletic type, they are frequently fair, blue-eyed and of even temperament On the contrary, the inhabitants of southern Spain are thin and swarthy Their eyes are dark and their teeth magnificent They are restless and superficial Nothing can better explain the contrast between these two groups than their different thyroid constitutions" One is further told that "during the critical involution period the other endocrine glands react anatomically and functionally thus compensating the insufficiency of the failing ovary This reaction is determined by temperament" "If a woman exhibits signs of a hypersuprarenal temperament, in the menopausal crisis those phenomena which we have given as probably dependent on hypersuprarenalism will predominate This temperament is, like the hyperthyroid, very frequent"

Maranon (p 103) lists among other factors which influence the chronologic climacteric "the color of the hair" One is further told that "very dark women are almost always hyperthyroid, hyperpituitary and hyperovarian" Evidence for this statement is cited from a novelist, Becquer In fact, illustrative material is cited almost as frequently from novels as from the medical and scientific literature or the author's own practice For example, the case of Sarah, the wife of Abraham, is referred to as "the oldest known case of post-climacteric conception" In connection with the hair (p 127) "sexual impulse causes curled hair, in both men and women, especially in certain mentalities of elemental sexuality and little

delicacy" While criticizing the freudian school in certain aspects, the author at times seems to outdo even the freudians For example, one is told "man's social status has a sex value His business and professional success is a means of sexual attraction"

In the chapters dealing with the general etiology of menopause symptoms, the author is hypothetic and verbose The actual descriptions of the symptoms are diffuse and contains too much duplication, but the poor quality of the book is probably best indicated in the chapters on the treatment of climacteric symptoms He recommends ovarian therapy by mouth, and states that "the results of ovarian therapy in the climacteric are excellent in general" As treatment for the alleged hyperthyroidism of menopause he recommends the defunct "antithyroid serum" The reviewer wonders where the author and the American editor have been the last twenty years As general therapy for menstrual disturbances of the climacteric, the author recommends the following regimen "1 Subject the patient to rest and institute general care of the uterine hemorrhages 2 Administer the usual classic remedies proper in these cases such as ergot, hydrastis, hamamezis, etc 3 Add, as a regulator of the ovarian function a discrete dose of ovarian extract" Such procedures will give no information on the influence of ovarian extracts

"The ovarian extracts, total or partial, have a positive hypotensive effect The existence of hypertension is therefore an indication for intensifying ovarian therapy" In cases of cardiac insufficiency during the climacteric he recommends the use of "whole ovarian extracts in vigorous doses" In asthenia of the climacteric one is told that "ovarian treatment is of indubitable usefulness" Pruritus is said to "respond perfectly to ovarian opotherapy" Obesity during the climacteric also "yields well to ovarian opotherapy" And finally, in the paragraph on the therapy of masculine climacteric, the author says that he has "employed ovarian extracts in men with good results"

Contrast this endocrine euphoria of Dr Maranon with sober clinical conclusions of Dr Novak (Glandular Therapy, American Medical Association, 1925) "rational as ovarian therapy appears to be in some conditions, the results are rarely striking and often nil, to the level-headed observer It cannot be assumed that a commercial extract can replace the normal ovarian secretion in the patient's body, or, for that matter, that it originally contains any of the active hormones of the ovary Here lies the crux of the whole problem, whose solution will depend in large measure on the work of the biochemist Until this day, the physician who uses ovarian therapy should keep his feet on the ground and not let himself be carried away by the exaggerated claims of those who have something to sell, or the ill advised and premature reports of honest but deluded professional colleagues who have not yet learned the dangers lurking in the 'post hoc propter hoc' method of reasoning"

This monograph of Maranon advances neither medical science nor medical practice It is amusing and easy reading if the busy practitioner is willing to wade through reams of verbosity and waste much time in hunting down the old and established facts in a jungle of fiction

## DISEASES OF THE LIVER

### VIII THE VARIOUS TYPES OF SYPHILIS OF THE LIVER WITH REFERENCE TO TESTS FOR HEPATIC FUNCTION<sup>4</sup>

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CARL H GREENE, M D

AND

LEONARD G ROWNTREE, M D

ROCHESTER, MINN

The protean nature of syphilis is nowhere better illustrated than by a consideration of its visceral manifestations, in fact, the recognition of visceral syphilis by clinical means alone is often difficult if not impossible. In consequence, great emphasis has been placed on those laboratory procedures which are of assistance in showing the presence of syphilitic infection.

Although serologic tests are of great value in the recognition of visceral syphilis, they do not tell which organ is involved, or the degree of injury produced by the syphilitic process. Such information, on the other hand, would be of inestimable value in diagnosis, prognosis and treatment. Particularly is this true in cases of syphilis of the liver. Additional diagnostic measures are desirable, and the recent interest in tests for hepatic function is evidence of the need for such information.

Recent studies of the physiologic activities of the liver have served to emphasize its manifold functions. Many of them are but imperfectly understood as yet. A test has not been devised for estimating the sum of the various activities of this organ. It is not surprising, then, that there have been great differences of opinion regarding the clinical value of the various proposed tests of hepatic function. We wish to report our experiences with certain of these tests in the study of syphilitic disease of the liver and our observations regarding their behavior in patients without a previous history of disease of the liver, in whom hepatic complications developed following treatment for syphilis.

We have studied more than 100 cases of syphilis complicated by various forms of hepatic disease. In many it has been possible to make repeated studies over periods varying from six months to six years.

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\* Submitted for publication, Feb 11, 1929

\* From the Section on Dermatology and Syphilology and the Division of Medicine, the Mayo Clinic and the Mayo Foundation



The diagnosis has been made, for the most part, on the basis of clinical impressions and the effect of therapeutic tests. In some cases, laparotomy or necropsy has permitted of a positive pathologic diagnosis.

It is obviously impossible to present so varied a mass of material without careful consideration of the clinical features of the disease as well as of the different laboratory tests. Syphilis of the liver, in its clinical manifestations at least, is not a common complication of syphilis. During the last ten years, 171 patients with various forms of hepatic syphilis have been seen in the Mayo Clinic. This gives an incidence of approximately one in 2,000 medical and surgical admissions. Estimated with relation to syphilis, hepatic complications of one form or another are to be observed in less than 1 per cent of the syphilitic patients in the Mayo Clinic. The incidence of hepatic syphilis is probably greater than these figures indicate, as evidenced by the finding of previously unrecognized syphilitic lesions in the liver at necropsy, and also by the frequency with which dormant hepatic syphilis becomes symptomatic during or following antisymphilitic treatment. McCrae<sup>1</sup> reported an incidence of hepatic syphilis of 0.2 per cent recognized clinically, and 1.5 per cent found at necropsy. It appears that approximately 2 per cent of syphilitic patients under treatment will develop one or more manifestations of hepatic complication. Various estimates of the serologic data show that in approximately 90 per cent of the patients with hepatic syphilis the Wassermann reaction of the blood is positive.

The following classification of syphilitic disease of the liver, modified from that suggested by Stokes,<sup>2</sup> has been used in this study.

#### Acute Syphilis

- 1 Hepatitis of acute syphilis (benign)
- 2 Acute yellow atrophy (severe)

#### Late Syphilis

- 1 Asymptomatic
- 2 Diffuse hepatitis of late syphilis
- 3 Gummatous hepatitis (hepar lobatum)
- 4 Chronic hepatitis or syphilitic cirrhosis
  - (a) Chronic hepatitis with jaundice (biliary cirrhosis)
  - (b) Chronic hepatitis with ascites (portal cirrhosis)

#### Hepatic Complications of Treatment for Syphilis

- 1 Postarsphenamine jaundice (arsenical or infectious)
- 2 Icterus gravis or acute yellow atrophy of the liver
- 3 Hepatorecurrence and Herxheimer effect in the liver
- 4 Treatment cirrhosis
- 5 Jaundice associated with malarial inoculation

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1 McCrae, Thomas. Tertiary Syphilis of the Liver, *Am J M Sc* **164** 625, 1912.

2 Stokes, J. H. *Modern Clinical Syphilology*, Philadelphia, W. B. Saunders Company, 1926, p. 1144.

In this study we present a record of our personal experience and opinion rather than a detailed discussion of the clinical and pathologic features of these various types of hepatic syphilis. The details must be sought in the writings of Lancereaux,<sup>3</sup> Fournier,<sup>4</sup> Osler,<sup>5</sup> Hutchinson,<sup>6</sup> Rolleston,<sup>7</sup> McCrae,<sup>8</sup> Stokes,<sup>2</sup> Wile<sup>9</sup> and others. Instead, we present a summary of the essential clinical features of the different conditions, together with abstracts of the histories of illustrative cases. The complete laboratory data are given in the accompanying tables.

This study was started six years ago, and the majority of the tests considered of value in estimating hepatic function since that time have been utilized. In the beginning, emphasis was placed on the fructose tolerance test, the nitrogen partition in the blood, the determination of the serum bilirubin content and the phenoltetrachlorophthalein test. Later, the bromsulphalein test and the determination of the bile acids in the blood were added. The technic of these various tests already has been reported in<sup>10</sup> detail<sup>11</sup> although we have slightly modified the bromsulphalein test. Rosenthal and White<sup>12</sup> recommended the injection of 2 mg of bromsulphalein to each kilogram of body weight. We have found a dose of 5 mg for each kilogram more satisfactory in routine use. Succeeding blood samples are then taken fifteen, thirty and sixty minutes after the injection of the dye. A positive Wassermann reaction, the Kolmer technic being used, was obtained in either the blood or the spinal fluid in all cases included in the study. In consequence, specific notation of this test has been omitted from the tables.

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3 Lancereaux, Etienne. *A Treatise on Syphilis, Historical and Practical*, London, New Sydenham Society, 1868-1869.

4 Fournier, Jean-Alfred. *The Treatment of Syphilis*, New York, Rebman Company, 1906, p 219.

5 Osler, William, Churchman, J W, and Conner, L A. Syphilis, in Osler, William, and McCrae, Thomas. *Modern Medicine*, ed 3, Philadelphia, Lea & Febiger, 1925, p 389. Osler, William, and Gibson, A G. Visceral Syphilis, in D'Arcy, Power, and Murphy, J K. *A System of Syphilis*, London, Oxford University Press, 1914, vol 3, p 1.

6 Hutchinson, Jonathan. *Syphilis*, London, Cassell & Company, 1901, p 532.

7 Rolleston, H D, and McNee, J W. *Diseases of the Liver, Gall-Bladder and Bile Duets*, ed 3, New York, The Macmillan Company, 1929, p 884.

8 McCrae, Thomas, and Caven, W R. Tertiary Syphilis of the Liver, *Tr A Am Phys* **41** 168, 1926.

9 Wile, U J. Syphilis of the Liver, *Arch Dermat & Syph* **1** 139 (Feb) 1920.

10 Greene, C H, Snell, A M, and Walters, Waltman. Diseases of the Liver I. A Survey of Tests for Hepatic Function, *Arch Int Med* **36** 248 (Aug) 1925.

11 Aldrich, Martha, and Bledsoe, Mary Sue. Studies in the Metabolism of the Bile. I. A Quantitative Pettenkofer Test Applicable to the Determination of Bile Acids in the Blood, *J Biol Chem* **77** 519, 1928.

12 Rosenthal, S M, and White, E C. Clinical Application of the Bromsulphalein Test for Hepatic Function, *J A M A* **84** 1112 (April 14) 1925.

## SYPHILIS WITHOUT APPARENT INVOLVEMENT OF THE LIVER

In the course of this study we tried the various tests for hepatic function in a number of patients with syphilis in whom there was no involvement of the liver. Many of these patients had late syphilis of the central nervous system or of the cardiovascular system. They did not present symptoms referable to the liver, and there was no enlargement or other evidence of hepatic involvement. In a few, exploratory laparotomy had been performed, at which time the liver appeared to be normal. This series served as a control, and normal results were obtained throughout (table 1). The serum bilirubin content varied between 0.1 and 1.5 mg, and an indirect van den Bergh reaction was obtained. The phenoltetrachlorophthalein reading varied between 3 and 9 per cent in the one hour sample, and the bromsulphalein between 0 and 8 per cent in the half hour sample. The Pettenkofer reaction gave a value for the bile acids between 4 and 5.2 mg. These values correspond well with the usually accepted range for the normal.

## HEPATITIS OF ACUTE SYPHILIS

The diffuse hepatitis of acute syphilis is a rare complication of the disease. Wile and Karshner,<sup>13</sup> who reviewed this subject, called attention to the fact that it appears in two forms: the mild type associated with jaundice, malaise and enlarged liver appearing simultaneously with the secondary eruptions, and the severe type which, as a rule, progresses to acute yellow atrophy and death. The presence of the clinical evidence of acute syphilis, together with jaundice and its attendant symptoms, lead to the presumptive diagnosis. We are able to report the case of a patient in whom a moderate degree of hepatitis developed in connection with the appearance of mucous patches and a maculopapular syphilitid and in whom the jaundice promptly disappeared following judicious anti-syphilitic treatment.

CASE 31 (table 2) —A hair-dresser, aged 21, acquired a chancre in November, 1927. Four weeks later, a florid, papular, secondary eruption developed. Jaundice appeared a few days later. She came to the clinic on Dec. 28, 1927, three weeks after the onset of the jaundice.

At the time of examination the patient had an acute, papular, secondary rash and mucous patches (condyloma latum). A dark-field examination of the lesions was positive for the *Spirochaeta pallida*. The Kolmer modification of the Wassermann reaction on the blood also was positive and was graded 44.<sup>14</sup> There

13 Wile, U. J., and Karshner, R. G. Icterus Gravis Syphiliticus. Its Relation to Acute Yellow Atrophy, J. A. M. A. 68:1311 (May 15) 1917.

14 By this method of grading is indicated the result of a set-up of three tubes, of which the third is a control and the first two are read. The result "44" means that in the first tube, which contained 0.1 cc. of patient's serum, and also in the second tube, which contained 0.05 cc. of patient's serum, the result was ++++

TABLE 1—*Syphilis Without Apparent Involvement of the Liver*

## PART 1

Case	Date	Age, Years	Sex	Edge of Liver Palpable, Cm	Blood Nitrogen Partition, Mg for Each 100 Cc					Non-protein Nitrogen, Jaundice	Serum Bilirubin, Mg for Each 100 Cc	Van den Bergh Direct Reaction	Phenoltetraethlorphthalen Test			True tose Tolerance Test	Diagnosis
					Urea	Uric Acid	Creatinine	Amino Acid Nitrogen	Dye in Serum, per Cent								
									15 Min				1 Hour	2 Hours	Dye in Urine, Mg		
1	11/12/24	37	M	0	27	3.5	1.3	6.6	0	0.7	0	0	13	9	3	0 0	Neurosyphilis
2	8/25/25	53	M	0	42				0	1.1	0	0	10	8	5		Neurosyphilis
3	10/9/25	40	F	+					0	1.5	0	0	10	3	1		Neurosyphilis
4	8/18/25	43	F	0	26				0	0.2	0	0	8	3	0		Neurosyphilis
5	9/9/24	52	M	0	46	3.0	1.7	6.8	0	0.6	0	0	8	4	2	0.2	Latent syphilis
	9/30/24				33	2.7	1.5	5.4	0	0.6	0	0	7	3	0	0.0	
6	6/30/21	38	M	0	34	3.3	1.4	6.4	0	0.9	0	0	7	4	1	0.0	Neurosyphilis
7	6/18/21	42	M	0	33	2.6	1.6	5.6	0	0.7	0	0	7	3	2	0.1	Paresis, neurosyphilis
	7/7/21				40	4.0	1.6	7.0	0	0.7	0	0	7	4	2	0.2	
8	10/22/21	39	F	2	21	2.2	1.4	6.3	0	1.1	0	0	6	3	2	0.6	Neurosyphilis
9	6/24/24	20	F	0	34	3.9	1.5	6.1	0	0.6	0	0	7	3	0		Acute syphilis
10	7/23/21	47	F	0	48	3.5	1.3	6.9	0	1.0	0	0	6	3	1		Neurosyphilis
11	3/25/25	37	M	+	19	3.2	1.3		0	0.6	0	0	6	3	0		Neurosyphilis, paresis
12	2/12/26	40	M	0					0	0.6	0	0	5	5	3		Latent syphilis
13	6/24/21	52	M	0	105	4.6	1.7	6.8	0	0.6	0	0	5	3	0	0.0	Neurosyphilis
	6/30/21				54	69	1.8	6.4	0	0.9	0	0	4	3	0	0.0	
14	10/21/24	68	M	0	27	2.2	1.5	7.7	0	0.2	0	0	5	2	1	0.0	Acute syphilis
15	9/20/24	48	M	0	28	2.8	1.6	6.5	0	0.6	0	0	5	3	0	0.5	Neurosyphilis
16	4/7/24	42	M	0	35				0	1.3	0	0	4	2	0	0.3	Latent syphilis

## PART 2

Case	Date	Age, Years	Sex	Edge of Liver Palpable, Cm	Jaundice	Blood Urea, Mg for Each 100 Cc	Serum Bilirubin, Mg for 100 Cc	Van den Bergh Reaction	Bile Acids, Mg for 100 Cc of Blood	Bromsulphalein Test, Dye in Serum, per Cent			Galactose Tolerance Test	Diagnosis
										15 Mm-utes	30 Mm-utes	60 Mm-utes		
										15 Mm-utes	30 Mm-utes	60 Mm-utes		
17	11/23/27	51	F	2	0	16	0.3	0	5.2	8	8	4	0	Latent syphilis
18	1/12/28	44	F	0	0	33	0.2	0	4.6	8	8	2		Neurosyphilis
19	9/1/28	53	M	0	0	27	0.3	0		6	6	2		Neurosyphilis
20	7/21/28	40	M	0	0	21	1.2	0		4	4	0		Neurosyphilis
21	5/15/28	37	M	0	0	26	1.1	0	4.8	4	4	1		Neurosyphilis, tabes
22	1/21/28	36	M	3	0	24	0.2	0	4.3	4	4	0		Neurosyphilis
23	12/28/28	56	M	0	0	26	0.7	0		2	2	0		Neurosyphilis
24	4/4/28	44	F	1	0	28	0.2	0		2	2	0		Neurosyphilis
25	10/20/26	39	M	0	0	28	0.2	0	4.0	1	1	0		Neurosyphilis
26	4/23/27	49	M	0	0	28	0.6	0		5	5	0		Neurosyphilis
27	4/15/25	59	F	0	0	23	0.5	0		0	0	0		Latent syphilis
28	5/5/25	52	F	0	0	24	0.2	0	4.3	0	0	0		Neurosyphilis
29	4/20/27	42	F	0	0	24	0.9	0		0	0	0		Latent syphilis
30	1/11/23	35	M	0	0	16	0.2	0	4.8			0		Neurosyphilis

was a moderate degree of jaundice, and the serum bilirubin was 7.9 mg in each 100 cc. The patient was given a course of mercury rubs. This was followed by rapid fading of the jaundice and coincident disappearance of the lesions of the skin. The serum bilirubin content dropped to normal by Jan. 12, 1928. Thereafter the patient remained well.

The laboratory tests showed a characteristic curve of recovery. The serum bilirubin, which was moderately increased, rapidly returned to normal. A direct van den Bergh reaction was present at first, and this persisted for a considerable period after the serum bilirubin had returned to the normal level. There was no increase in the bile acids. The bromsulphalein test showed marked retention of dye during the period of jaundice. This returned to normal more slowly than did the serum bilirubin. The final examination, eight months after the onset of the icterus, showed normal responses to all tests.

TABLE 2 (case 31) —*Progress in an Illustrative Case of Hepatitis of Acute Syphilis*

Date	Blood Urea, Mg. for Each 100 Cc.	Serum Bilirubin, Mg. for Each 100 Cc.	Van den Bergh Direct Reaction	Bile Acids, Mg. for Each 100 Cc. of Blood	Bromsulphalein Test, Dye in Serum, per Cent		
					15 Minutes	30 Minutes	60 Minutes
12/29/27	14	7.9	+	5.1		64	64
1/3/28		4.4	+				
1/12/28	23	1.6	+	4.6		36	26
1/23/28	16	0.8	+	4.8		12	10
2/4/28		0.2	+	4.4		4	2
2/21/28	25	0.1	+			6	2
7/23/28	25	0.2	0			4	4

DIFFUSE HEPATITIS OF LATE SYPHILIS

The hepatic complications associated with secondary syphilis present a fairly uniform clinical picture. The hepatitis of late syphilis is variable, but Wile<sup>15</sup> called attention to the point that the various clinical manifestations of late hepatic syphilis are due to different phases in the evolution of the morbid process. Our experience confirms this view. From a clinical point of view, late hepatic syphilis may be classified into two groups: hepatitis, the active process, which may be diffuse, gummatous or of mixed character, and cirrhosis, the end-result. All degrees and modifications or combinations may be present, the symptoms depending on the extent and degree of localization of the destruction of hepatic tissue.

The clinical syndrome of diffuse syphilitic hepatitis is identical with that of the nonsyphilitic forms of hepatitis which are caused by infec-

15 Wile, U. J. Two Unusual Phases of Hepatic Syphilis, Arch. Dermat. & Syph. 1: 656 (June) 1920, The Treatment of the Syphilitic Liver and Heart. A Therapeutic Paradox, Am. J. M. Sc. 164: 415, 1922.

tious, chemical or toxic agents. Hence, it is essential that collateral evidences of syphilis be demonstrated before it is assumed that the hepatic disease is of syphilitic origin. Recently, both Stokes and McCrae discussed the symptoms of hepatic syphilis, but only in the gummatous type do the clinical data indicate the syphilitic nature of the condition. In certain instances, prolonged periods of observation and treatment are necessary to permit of etiologic deductions, in others, the postmortem examination alone furnishes a basis for a final conclusion.

The diffuse form of hepatitis makes a most favorable response to treatment with mercury and potassium iodide. The use of mercury by mouth in small doses, a form of treatment now used by syphilologists only when stimulative effects are desired, is an advantageous way in which to start antisyphilitic treatment in these patients. This may be augmented in a few weeks by inunction, or by the intramuscular injection of a soluble mercurial salt. This mild form of treatment permits of a slow and gradual replacement fibrosis in the liver, at the same time, it allows full opportunity for the establishment of collateral circulation of the blood. Under such circumstances the use of the arsphenamines is contraindicated, a point noted by others. The injudicious administration of arsenical preparations in this type of case may lead to the rapid production of portal cirrhosis and marked hepatic insufficiency. The characteristics of the whole group may be seen in table 3. The following case is an example of this type of diffuse hepatitis.

CASE 38 (table 3).—The patient came to the clinic in June, 1923, because of a history of gallstone colic. At admission he was found to have a slightly enlarged liver, and roentgenograms of the gallbladder showed the presence of stones. At the same time, the Wassermann reaction of the blood was positive. He received a course of antisyphilitic treatment consisting of six intravenous injections of arsphenamine, a total of 2.8 Gm, and twenty-nine intramuscular injections of succinimide of mercury of  $\frac{1}{6}$  grain (0.0108 Gm) each. At the end of this course of treatment the edge of the liver was still readily palpable and extended one fingerbreadth below the costal border.

The patient was operated on on August 9, because of severe gallstone colic which developed during the course of the antisyphilitic treatment. At the operation, gallstones were found, in addition to diffuse hepatitis which the surgeon reported as probably syphilitic in nature.

Following an uneventful convalescence the patient was sent home, but he returned again in November, 1923, for further treatment. Bile was found in the urine at this time. During November and December he received six intravenous injections of arsphenamine for a total of 2.1 Gm and six intramuscular injections of 1 grain (0.065 Gm) each of an insoluble mercurial salt. In March, 1924, he reported that marked jaundice had developed. The jaundice persisted until the time of his return in May. Six duodenal lavages gave a fair return of bile but only slight symptomatic relief. It was believed that syphilitic hepatitis was the cause of his difficulty, and he was given twenty intramuscular injections of succinimide of mercury of  $\frac{1}{6}$  grain (0.0108 Gm) each in conjunction with potassium iodide. The icterus disappeared. Following an interval of six months he

TABLE 3—Diffuse Hepatitis of Late Syphilis

PART 1

Case	Date	Age, Years	Sex	Edge of Liver Palpable, Cm	Jaundice, Graded 0 to 4	Duration of Jaundice, Mos	Spleen Enlarged, Graded 0 to 4	Blood Nitrogen Partition, Mg for Each 100 Cc	Urea	Uric Acid	Creatinine	Amino Nitrogen	Serum Bilirubin, Mg for Each 100 Cc	Van den Bergh Reaction	Phenolphthaleinchlorophthalin Test	True Toxicance Test	Comment		
32	5/28/21 6/1/21	36	M	0	1	1	0	39	49		17	68	9.4	+	35	11	7	10	Improving
33	6/16/21	44	M	0	0	0	41	38	19	21	63	2.0	0	0	24	20	3	20	Jaundice cleared Neurosyphilis
	6/24/21			0	0	0	37	39	22	19	58	0.6	0	0	8	2	0	06	
	10/22/21			+	4	4	29	20	27	15	64	16.3	+	24	24	20	31		
	11/5/24				4	3	33	27	27	08	66	10.9	+	24	22	14	26		
34	11/20/21	38	M		3	3	29	17	26	11	61	6.4	+	20	20	18	30	Improving slowly	
	12/12/21				2	2	29	20	31	13	59	5.1	+	22	25	22	25		
	1/24/25				1	15	0	23	29	16		37	+	20	21	17			
35	2/18/25 7/21/24	42	M	0	1		0	24	28	12	59	3.2	+	16	22	13		Improving Latent syphilis, jaundice clearing	
36	1/13/25	54	M	2	1	1	0	25				1.0	±	8	3	3		Neurosyphilis, jaundice nearly gone	
37	8/5/21	49	F	10	0	0	34	23	23	14	63	0.5	0	10	9	3	0.1	Latent syphilis, jaundice cleared	
	8/9/24			10	0	0	30	26	23	12	18	0.6	0	13	9	2	0.1	Laparotomy for other cause, diagnosis confirmed	
38	5/6/21	46	M	8	2	15	+	22	38	19	61	9.7	+	23	36	26	25	Laparotomy for other cause, diagnosis confirmed	
	5/24/21																	Improving with treatment (continued in part 2)	
	6/10/24			2	2		24	26	32	10	59	9.1	+	22	25	24	10		
	11/24/24			+	1	0	29	25	21	14	55	6.4	+	11	11	13	06		
	6/20/25							53	12	19		1.1	+	12	7	3	06		
								44				1.7	+	9	7	0			

PART 2

Case	Date	Age, Years	Sex	Edge of Liver Palpable, Cm	Jaundice, Graded 0 to 4	Duration of Jaundice, Months	Spleen Enlarged, Graded 0 to 4	Blood Urea, Mgm for Each 100 Cc	Serum Bilirubin, Mg for Each 100 Cc	Van den Bergh Reaction	Bile Acids, Each 100 Cc of Blood	Bromsulphalein Test, Dye in Serum, per Cent	15 Minutes	30 Minutes	1 Hour	Comment	
38	1/24/27	49	M	+	1	3	2	0	1		0.8	0	6.1		10	2	Syphilitic hepatitis, recovered
39	5/20/26	32	M					20	20	21.4	21.4	+	+				Syphilitic hepatitis
	5/21/26							25	25	18.3	18.3	+	1.8		90	61	
40	5/23/26	46	M					30	30	10.3	10.3	+					Improving
	7/2/26							25	25	12	12	+	3.4		100	61	
41	2/27/28	46	M	5	2	10	1	1	0		7.2	+			10	0	Free of jaundice for 1 month
	8/23/27				1		0	41	0		52	+			68	68	Syphilitic hepatitis
	1/18/28							29	52	22	22	+					Syphilitic hepatitis
	2/9/28			1	1		0	32	22	16	16	+	6.2		36	34	
42	3/1/28	51	F					23	23	11	11	+	7.0		30	30	Improving with treatment
	8/6/23							14	14	11	11	+			30	30	Three years after recovery
	1/4/27			0	0		0	38	38	0.8	0.8	+			26	20	
	6/17/28							17			0.2	0	4.5		14	12	
43	6/17/28	41	M												0	0	Three years after recovery

took forty mercurial inunctions. During July and September, while at home, the patient had two attacks of jaundice, each lasted about a month, and both subsided following a course of mercury intramuscularly. Since June, 1925, frequent examinations, in conjunction with the use of mercurial inunctions and potassium iodide, have maintained good health.

The functional tests are recorded in table 3.

When the patient was seen in May 1924, the serum bilirubin content was elevated, 97 mg in each 100 cc, and there was a direct van den Bergh reaction. The serum bilirubin decreased rapidly as the jaundice cleared. When the patient was seen in November, 1924, the serum bilirubin was normal and it has remained so. The direct van den Bergh reaction persisted for a considerable period after the serum bilirubin had returned to normal, but eventually it was replaced by the indirect reaction. The phenoltetrachlorophthalein test showed a marked retention of dye during the period of jaundice. This slowly decreased, and a normal reaction was found in June, 1925. A bromsulphalein test in January, 1927, likewise gave a negative reaction. A negative reaction was obtained in the fructose tolerance test during the period when the patient was still jaundiced.

This patient had syphilitic hepatitis in addition to the gallstones. He was treated with arsphenamine and mercury, following which jaundice and clinical signs of mild hepatitis developed. Under the continued use of mercury and potassium iodide he responded favorably, from both the clinical and the laboratory standpoint. Observation over a period of five years warrants a diagnosis of diffuse syphilitic hepatitis.

#### GUMMATOUS HEPATITIS (HEPAR LOBATUM)

Gummatous involvement of the liver, especially when it takes the form of a typical *hepar lobatum* (table 4), offers the most readily diagnosed clinical picture of hepatic syphilis and the one most frequently suspected from clinical observations. Carcinoma, abscess, cystic disease, simple hypertrophy, cholelithiasis and splenomegaly at times offer difficult differential problems. In such cases, a final diagnosis must be made in part by exclusion and in part by the aid of the various laboratory tests available. When the patient has milary gummas which do not enlarge the liver sufficiently to make it palpable, clinical differentiation is much more difficult than when a nodular or botryoid liver is present. Clinical differentiation of diffuse syphilitic hepatitis and milary gummas may be impossible. Similarly, patients with gummatous livers, as a rule, have also varying degrees of diffuse scarring or cirrhosis. When ascites develops in such cases the differential diagnosis of gummatous hepatitis and portal cirrhosis may be exceedingly difficult. Treatment, as in diffuse syphilitic hepatitis, should be mild and the response to mercury and iodides is excellent. The following case demonstrates the value of such treatment. The arsphenamines alone are not indicated in the treatment for this form of hepatic syphilis. When other complications demand their use, it must be recognized that unusual circumstances are present, and corresponding care must be taken.



TABLE 4—*Gummatous Hepatitis*

## PART 1

Case	Date	Age, Years	Sex	Liver En- larged, Graded 0 to 4	Blood Nitrogen Partition, Mg for Each 100 Cc					Serum Bili- rubin, Mg for Each 100 Cc	Van den Bergh Direct Reac- tion	Phenoltetraephthal- ein Test					True tose Toler- ance Test	Comment	
					Non- protein Nitro- gen	Spleen En- larged	Liver Nod- ular	Uric Acid	Creat- inine			Amino- Acid Nitro- gen	Dye in Serum, per Cent						
													15 Minutes	1 Hour	2 Hours	Dye in Urine, Mg			
44	8/18/25	42	F	1	+	0		23		1 1	±	17	17	10	0 5	Gumma found at operation in 1924, now healed			
45	6/18/25	66	M	2	0	0		44		1 6	±	17	9			Asciates			
46	7/31/25	36	M	2	+	0		27		0 3	0	15	13	8					
47	1/28/25	43	F	3	+	+		24		1 2	0	15	5	5		Gumma of liver			
48	2/25/25	41	F	0	0	0		25	1 8	0 5	0	12	3	0		Gumma in 1917, now healed			
49	11/ 4/25	38	M	2	0	0		24		0 8	0	8	3	0					
50	8/ 4/24	51	F	2	0	0		27	1 4	5 8	0	7	3	0	0	Gumma found at operation in 1910, now healed			
51	8/21/24					38		13	2 6	4 4	0	8	3	0	0				
51	3/24/25	36	M	3	+	++		46	1 5	0 7	0	7	0	3		Gumma found at necropsy, asciates			
52	9/ 9/24	44	M	2	+	0		30	1 3	5 8	0	11	7	5		Improving with treatment			
11/19/24				1	+	0		34	1 2	6 9	0	15	6	0	0 8				
12/ 2/24						28		37	1 1	6 8	0	12	5	2					
4/ 1/25		45						41		0 6	0	12	7	2	0 9	(continued in part 2)			

## PART 2

Case	Date	Age, Years	Sex	Liver Enlarged, Graded 0 to 4	Spleen Enlarged, Graded 0 to 4	Blood Urea, Mg for Each 100 Cc	Serum Bilirubin, Mg for Each 100 Cc	Van den Bergh Direct Reaction	Bile Acids, Mg for Each 100 Cc Blood	Bromsulphalein Test Dye in Serum, per Cent			Comment	
										15 Minutes	30 Minutes	1 Hour		
52	9/ 9/27	47	M	1	+	22	0.3	0			14	4	Gumma in 1924, now healed	
53	7/ 9/25	36	M	2	+	15	0.4	0			20	6	Gumma of liver	
	4/ 1/26	37				25	0.5	0	3.9		36	8	Later, after treatment	
	8/15/27	38				34	0.9	0				28	8	
54	9/15/28	39	F	2	+	30	0.9	0				14	4	Gumma of liver
	6/22/26	45					0.6	0				20	12	Later, after treatment
55	7/31/26	44	M	1	+	0	0.6	0	4.4			10	0	Gumma found at operation
56	12/16/26	43	F	2	0	36	0.2	0	4.2			18	12	Gumma of liver
	7/10/25				+	24	0.2	0			8	4	0	Later, after treatment
	6/16/26	44					0.5	0	6.3			20	3	
	6/23/27	45				27	0.5	0				2	0	
57	12/21/27	39	F	0	0	32	0.2	0	5.1			8	0	Gumma in 1917, now healed
58	10/20/26	47	F	4	0	13	0.3	0				4	0	Gumma of liver
	3/ 1/27				+	17	0.5	0	3.6			14	8	Later, after treatment
	11/ 3/27	48		2	1	31	1.0	0				2	0	
	9/19/28	49		4	+		1.1	0				6	2	
59	6/16/26	40	F	0	0		0.7	0				4	2	Gumma found at operation in 1920, now healed

CASE 52 (table 4) —The patient came to the clinic in September, 1924, complaining of soreness in the right upper quadrant of the abdomen and gave a history that during the last four years he had had frequent attacks of pain in the upper part of the right side of the abdomen, with soreness and tenderness on pressure in the region of the liver. Even a deep breath would cause discomfort. Gastro-intestinal upset or loss of appetite had not been noted, and there was not any history of chills, fever or jaundice. He had lost about 10 pounds (4.5 Kg) in weight.

General examination showed the edge of the liver to be 5 cm below the costal margin, with palpable irregular nodules on the border. The spleen apparently was not enlarged. The Wassermann reaction of the blood was strongly positive, and results of examination of the spinal fluid were negative. The patient did not receive arsphenamine at any time, the treatment consisted solely of mercurial inunctions and iodides. The subcostal mass rapidly disappeared under treatment, and the patient now weighs more than his previous maximal weight and is in good general condition.

This case demonstrates the value of treatment by mercurials and iodides in gummatous hepatitis. The arsphenamines are not indicated in the treatment for this form of hepatic syphilis unless other complications of syphilis demand their use, and then only under extreme circumstances.

In the gummatous form of disease of the liver there are numerous circumscribed areas of destruction of tissue of the liver, and hence more effort at compensation is possible than in diffuse hepatic involvement. The frequency with which livers with gummatous involvement may become greatly enlarged before producing few and insignificant constitutional symptoms may be cited as an example of the efforts at compensation which are made by the body. If judiciously treated, this group of patients invariably gives a highly favorable therapeutic response to the use of mercury and potassium iodide. During treatment the serum bilirubin (table 4) decreased slightly in this case, but it at no time exceeded the usual limits of normal. None of the patients with gumma was jaundiced, and the serum bilirubin was not increased. An indirect van den Bergh reaction was obtained in all patients. The fructose tolerance test was done in two instances, with negative results. The bile acids in the blood were not increased. The phenoltetrachlorophthalein test showed slight retention of dye in the case cited, and there was no change during the course of treatment, for in the majority of the cases of gumma which were studied there was a slight retention of dye, whereas normal dye readings were obtained in the remainder. The presence of enlarged nodular livers in the majority of these cases indicated the presence either of well developed gummas or of the scars resulting from the healing of such lesions. With localized lesions of this type the remainder of the liver may be relatively intact and free from functional

interference Greene, McVicar, Rowntree and Walters<sup>16</sup> pointed out that in carcinomatous invasion of the liver the degree of abnormality in the various functional tests depends on the interference with activity of the liver as a whole Unless there is infringement of or reduction in the normal reserve, a localized lesion such as a metastatic nodule cannot be demonstrated by functional tests The same condition of affairs attends the demonstration of a gumma by these tests

#### CHRONIC HEPATITIS

The rôle played by syphilis in the development of hepatic cirrhosis has been a subject of great controversy In the past, especially before the introduction of the Wassermann test, syphilis frequently was thought to be one of the chief etiologic agents in hepatic disease, and the use of mercury and iodides in cases of cirrhosis of the liver was recommended almost as a routine We now recognize that there are many cases of cirrhosis in which there is no evidence, clinical, serologic or pathologic, of the presence of syphilis, and Greene, McVicar, Snell and Rowntree<sup>17</sup> recently reported a study of various tests for hepatic function in a series of cases of cirrhosis in which syphilis could be excluded as an etiologic agent Nevertheless, cirrhosis is often met with in cases of syphilis, and the possibility of an etiologic relationship should not be dismissed Both biliary and portal types of cirrhosis occur

#### CHRONIC HEPATITIS WITH JAUNDICE (BILIARY CIRRHOSIS)

In the discussion of the different forms of hepatic cirrhosis in nonsyphilitic cases the close relationship between cases of subacute hepatitis with jaundice and those of biliary cirrhosis without obstruction to the biliary passages was pointed out The same relationship is to be observed in the syphilitic patient We have distinguished the diffuse hepatitis of late syphilis from biliary cirrhosis of apparently syphilitic origin but recognize that the distinction probably is one of degree and stage of involvement and so is not clearly defined Jaundice, frequently intermittent in type, malaise, loss of weight, diffuse enlargement of the liver and increase in the serum bilirubin with dye retention are characteristic features of both Obviously when the condition has been so severe and of such duration as to permit of a diagnosis of cirrhosis, the prognosis is correspondingly more serious Care is necessary in the institution of therapeutic measures Treatment should be mild and

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16 Greene, C H , McVicar, C S , Rowntree, L A , and Walters, W Diseases of the Liver IV Functional Tests in Cases of Carcinoma of the Liver and Biliary Tract, *Arch Int Med* **36** 542 (Oct ) 1925

17 Greene, C H , McVicar, C S , Snell, A M , and Rowntree, L G Diseases of the Liver VI A Comparative Study of Certain Tests for Hepatic Function in Cases of Cirrhosis of the Liver, *Arch Int Med* **40** 159 (Aug ) 1927

should be given cautiously to avoid too rapid fibrosis with consequent aggravation of the cirrhosis. The case reported is one of biliary cirrhosis in which it was possible to follow the whole course of development of this condition.

CASE 60 (table 5)—A married woman, aged 37, came to the clinic on Nov 26, 1923, deeply jaundiced and complaining of intermittent attacks of icterus for the preceding seventeen months. She gave a history of varying degrees of pain in the right upper abdominal quadrant, associated with clay-colored stools, dark urine, generalized pruritus and nausea. She had had six attacks of from two to three weeks' duration. She lost 14 pounds (6.4 Kg) in seventeen months.

On admission the patient was markedly jaundiced. The edge of the liver was felt 5 cm below the costal border, and the spleen was just palpable. The Wassermann reaction of the blood was reported strongly positive, but examination of the cerebrospinal fluid gave negative results. Roentgenograms of the stomach and gallbladder were negative. Mild secondary anemia also was present. The

TABLE 5 (case 60)—*Progress in an Illustrative Case of Syphilitic Cirrhosis Biliary Cirrhosis*

Date	Blood Urea, Mg for Each 100 Cc	Serum Bilirubin, Mg for Each 100 Cc	Van den Bergh Direct Reaction	Bile Acids, Mg for Each 100 Cc of Blood	Phenoltetrachlorophthalein Test				Bromsulphalein Test, Dye in Serum, per Cent			Fructose Tolerance Test
					Dye in Serum, per Cent			Dye in Urine, Mg	15 Min	30 Min	60 Min	
					15 Min	1 Hr	2 Hr					
11/26/23	10	13.1	+		30	26	23	2.5				
1/24/24	21	2.0	0		4	3	2	0.0				
4/16/24	13	4.8	±		23	25	20	2.2				0
8/19/24	19	9.2	+		24	26	26	3.2				
9/27/24	23	4.2	+		33	20	20	1.2				
12/ 2/24	32	3.0	+		15	13	8	1.2				
5/ 7/25		5.1	+		22	25	22	1.9				
6/ 6/25	11	8.2	+		24	18	16					
9/15/25	10	5.6	+		20	30	20	4.5				
4/ 6/26	33	6.8	+	6.8					40	36	32	
10/ 4/27		3.4	+	3.4						36	32	
8/27/28		5.1	+							40	36	

patient was given a month's preparation with mercurial inunctions and potassium iodide, and at the end of this time six injections of neoarsphenamine for a total of 2.9 Gm were given. She left the hospital on Feb 12, 1924, much improved and without signs of jaundice. The liver was slightly reduced in size, but the spleen was still palpable.

On April 14, 1924, the patient returned with moderate jaundice, although she had not had abdominal pain since the previous visit. The liver and spleen apparently were unchanged in size. A further course of mercury was instituted at home. She returned to the clinic on Aug 18, 1924, weighing 118 pounds (53.5 Kg), she had gained 12 pounds (5.4 Kg). The edge of the liver was hard and readily palpable. There was moderate jaundice with a serum bilirubin content of 9.2 mg in each 100 cc. Six intravenous injections of neoarsphenamine for a total of 2.6 Gm were given in conjunction with succinimide of mercury. At the end of this course of treatment the serum bilirubin content was reported as 4.2 mg. The next period of observation was in December, 1924, at which time the patient looked and felt much better than on any previous visit. The jaundice was somewhat less, and the serum bilirubin content was 3.0 mg. The next observation period was in May, 1925, when she returned slightly jaundiced. Another course

of mercury by mouth and six small doses of neoarsphenamine, a total dosage of 16 Gm, made her feel better, although there was no particular change in the degree of icterus. The Wassermann reaction of the blood remained positive. In September, 1925, she was still jaundiced. Both the liver and the spleen seemed somewhat enlarged. At this time she was given intramuscular injections of potassium bismuth tartrate with butyn, 0.2 Gm, once a week. The icterus entirely disappeared following this treatment and did not reappear until April of the following year when it gradually returned, associated with a sense of biliousness. The serum bilirubin content at that time was reported as 68 mg. Several periods of observation since have shown the same degree of retention of the dye and variations of serum bilirubin. Three periods of jaundice with spontaneous remissions have occurred, not associated with abdominal pain or colic. Roentgenograms of the gallbladder remain negative.

The outstanding change in this six year period has been a definite increase in the size of the liver and the spleen, constant retention of dye and increase in the serum bilirubin. The diagnosis was diffuse syphilitic hepatitis slowly progressing to the stage of hypertrophic cirrhosis.

The functional studies in this case have paralleled the clinical status. The value of frequent and repeated tests is exemplified in table 5. When the patient first was seen the bilirubin was markedly elevated, and there was a direct van den Bergh reaction and moderate retention of phenoltetrachlorophthalein. Under treatment, there was initially a return to normal as in the cases of diffuse syphilitic hepatitis previously discussed. When the patient was seen in April, 1924, the retention of dye was proportionally much greater than the increase in jaundice. This disproportion between the two readings we believe is evidence of the permanent injury to the liver associated with the development of cirrhosis. Since then there has been no significant change in the tests. The bilirubin has remained elevated, with a direct van den Bergh reaction, and there has been marked retention of both phenoltetrachlorophthalein and bromsulphalein.

#### CHRONIC HEPATITIS WITH ASCITES (PORTAL CIRRHOSIS)

Syphilis apparently was the chief etiologic agent in the cases of portal cirrhosis which we report in table 6, although in a few there was an additional history of chronic alcoholism. It is possible, too, that syphilis, although not of itself producing portal cirrhosis, may render the liver more susceptible to those noxious agents ordinarily responsible for the development of the latter condition. Finally, the effect of the modern intensive type of treatment for syphilis, particularly that with arsenical preparations, must not be overlooked as a cause of portal cirrhosis in such cases. This question will be discussed later in connection with the hepatic complications of treatment. Without more precise knowledge regarding the etiology of cirrhosis, it is manifestly impossible to make a more dogmatic statement. We are interested rather

TABLE 6—*Syphilitic Curiosis Portal Curiosis*

## PART 1

Case	Date	Age, Years	Sex	Edge of Liver Pal-Ascle, Graded 0 to 4	Dura- Spleen En- tion of larged, Graded 0 to 4	Jaun- dice, Graded 0 to 4	Non- protein Nitro- gen	Blood Nitrogen Partition, Mg for Each 100 Ce			Serum Bilirubin, Mg for Each 100 Ce	Van den Bergh Reaction	Phenoltrachlorphthalin Test			True tose Toler- ance Test	Comment
								Urea	Acid	Uric Acid			15 Min	1 Hr	2 Hr		
61	4/18/24	41	M	2	3	4	2	19	28	14	65	156	+	24	24	42	Jaundice, died 2 mo later
62	4/1/26	60	M	0	1	1	0	16	34	16	23	23	+	20	20	10	Necropsy
63	4/13/25	56	M	+	2	0	0	59	37	32	28	28	+	20	13	10	Died 3 months later
64	6/15/25	33	F	+	0	0	0	29	32	14	61	13	+	20	13	3	Ascle 7 years before
65	11/7/24	40	F	+	4	18	0	18	20	10	56	02	0	13	13	9	On admission
	12/10/24			+	0	+	+	21	20	10	56	02	0	13	13	9	Ascle free after treatment
66	5/22/24	62	M	0	3	1	0	150	47	19				12	10	6	Necropsy
67	7/4/23	50	M	+	2	2	0	32	31	16				10	10	6	Ascle 2 years before, died of hemorrhage
68	1/10/24	33	F	+	0	0	0	20			08	0		12	8	3	0
69	11/28/23	58	M	0	3	3	0	39						10	8	6	Died
70	1/21/24	41	M	0	4	11	2	33	60	90	59	07	0	10	1	1	04
71	11/13/24	43	F	0	3	1	0	114				06	0	10	1	0	Nephritis, died
72	9/8/23	47	M	+	2	48	0	24	24	10				7	1	0	Improved with treatment
73	3/12/25	41	M	+	3	5	1	21						10	12	8	0
	5/10/25			3	1		+	13			13	06	+	8	13	8	Ascle clearing up with treatment
	9/11/25			0	0		+	23			25	+		20	18	13	(continued in part 2)

## PART 2

Case	Date	Age Years	Sex	Edge of Liver Pal- Ascle, Graded Cm 0 to 4	Dura- tion of largo, Graded 0 to 4	Spleen En- larged, Graded 0 to 4	Jaun- dice, Graded 0 to 4	Blood Urea, Mg for Each 100 Ce	Serum Bilirubin, Mg for Each 100 Ce	Van den Bergh Direct Reaction	Bromsulphalein Test Dye in Serum, per Cent			Comment	
											15 Min	30 Min	1 Hour		
73	5/20/26	42	M	+	3	12	0	22	36	+	32	75	60	35	Necropsy, weight of liver 1,120 Gm Died of hemorrhage, necropsy
	9/9/26			+	3	+	1	42	68	+	37				
74	1/12/28	45	M	0	2	4	0	20	33	+	47			40	
75	4/1/26	60	M	0	1	+	0	19	38	+		95	75	50	
76	12/7/26	50	M	0	3	1	2	25	38	+	10		75	40	Died, necropsy
	12/13/26			+	1	+		28	26	+	10		42	30	
	12/27/26				5		0	26	27	+	35		40	30	
77	5/3/27	61	M	9	4	12	0	26	12	0	53		40	30	
78	10/3/25	41	M	0	3	36	0	37	22	+			41	20	Improvement with treatment
79	8/8/25	57	M	0	3	0	0	39	29	+		52	40	26	
80	7/29/26	60	M	7	4	1	+	20	10	0	43		24	14	
81	3/19/27	49	M	0	3	11	0	16	11	+	36		20	12	
82	11/10/26	50	F	1	2	3	+	25	24	0	32		18	14	Ascleites free Recurrence of ascleites
	11/19/26							33	27	0	38		32	16	
	11/22/26			1	2	3	0	33	23	0	32		22	12	
	11/30/26				3			43	20	0	29		28	16	
	12/7/26				1	0		20	11	0	45		14	6	Ascleites free Recurrence of ascleites
	12/13/26				0			64	08	0	30		14	2	
	12/21/26				3	0	0	32	12	0	50		32	22	
83	2/3/27	63	M	0	2	3	0	32	10	0	36		22	16	
84	11/18/26	33	F	3	1	5	0	27	07	0	28	36	18	18	Ascleites free Recurrence of ascleites
85	12/18/25	50	M	5	0	0	0	18	07	0	28		20	1	
	9/17/27				0			19	05	0	41		14	6	

in a study of the changes shown by the different functional tests and in the comparison between the changes found in the ordinary type of portal cirrhosis and the present group in which syphilis also is present

The degree of cirrhosis present at the time the disease is recognized clinically may be roughly estimated by the size of the liver, particularly if it is small, by the degree of ascites, it being borne in mind that ascites occasionally will occur early in the course of the cirrhosis, by the presence of pain in the right upper abdominal quadrant, by splenomegaly, and by jaundice. The presence of hematemesis, or blood in the stools is a complication to be dreaded—it suggests the presence of varices in the esophagus. In several of the cases in which therapeutic results were highly satisfactory the patients died suddenly from ruptured esophageal varicosities. The enlarged liver, and a slightly enlarged spleen, suggest early cirrhotic involvement in contrast to the small liver and large spleen which suggest extensive and long standing involvement. The treatment of a patient with such cirrhosis consists of the mild or tonic treatment for syphilis, aided by a diet with a low content of protein and a high content of carbohydrate, and by paracentesis when necessary. Antisyphilitic medication is a secondary consideration. The use of diuretics, as suggested by Rowntree, Keith and Barrier<sup>18</sup> has given symptomatic relief in advanced cases. The following history is an example of such a case of portal cirrhosis of apparently syphilitic origin.

CASE 73 (table 6) —A man, aged 38, with a history of alcoholism came under our care in 1920 for treatment for early *tabes dorsalis*. He received, over a period of two and a half years, four courses of antisyphilitic treatment consisting of twenty-four intravenous injections of arsphenamine for a total dosage of 97 Gm, 200 mercurial inunctions, thirty-six intramuscular injections of succinimide of mercury,  $\frac{1}{6}$  grain (0.0108 Gm), with potassium iodide during each course of mercury. The clinical and serologic result was highly satisfactory. Enlargement of the abdomen and edema of the ankles were noted in 1925 while the patient was confined to a hospital elsewhere by a fractured fibula and tibia. Because of the history of syphilis, with previous treatment, he was given seven intravenous injections of arsphenamine together with intramuscular injections of mercuric salicylate while he was convalescing from the fracture. Just before dismissal from the hospital, abdominal paracentesis had been done, following this, he returned to work and did not have any abdominal discomfort for six months.

The patient returned to the clinic in September, 1925, because of recurrence of the ascites. At that time the edge of the liver was 5 cm below the costal border in the nipple line, and there was a divergence of opinion as to whether the spleen was palpable or not. He was placed on a salt-free diet, with a fluid intake limited to 600 cc in twenty-four hours, and diuresis was induced with merbaphen. He improved considerably. He did not adhere to instructions after dismissal from the hospital, and again began drinking on the average of a quart of whisky a day. The ascites promptly recurred, and he returned in August, 1926, with

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18 Rowntree, L. G., Keith, N. M., and Barrier, C. W. Novasurol in the Treatment of Ascites in Hepatic Disease, *J. A. M. A.* 85:1187 (Oct 17) 1925.

marked ascites, the edge of the liver just palpable at the costal border and the spleen markedly enlarged. While under observation he bled to death from a ruptured esophageal varix.

Necropsy revealed a small liver (1,120 Gm) and an enlarged spleen (423 Gm). The liver presented typical Laennec's cirrhosis, there were many nodules of hepatic tissue with depressed areas of fibrous tissue between the nodules. The pathologic appearance was that of typical portal cirrhosis and without any features to indicate the specific etiologic agent responsible for its development. The ruptured esophageal varicosity was readily demonstrated in addition to other pathologic processes which had no bearing on this discussion.

The difficulty in determining the etiologic factor from the clinical syndrome is emphasized by this case report, also, the fact mentioned elsewhere that cirrhosis of the liver is the end-result of injury to the liver from various causes.

The laboratory determinations in this group of patients did not differ from those found in the series of cases of nonsyphilitic cirrhosis reported by Greene, McVicar, Snell and Rowntree.<sup>17</sup> The serum bilirubin was normal or slightly increased over the level found in that series in the majority of the cases of syphilitic portal cirrhosis. In the case cited, it was normal when the patient was first seen. As his condition advanced, there was an increase in the serum bilirubin to a value slightly over the normal. One patient with frank jaundice had correspondingly elevated serum bilirubin. A direct van den Bergh reaction was obtained in those cases in which the serum bilirubin was elevated and in some with a normal amount of pigment.

Retention of dye was observed in the cases of cirrhosis. A normal response was noted in only one instance. This was true of both the phenoltetrachlorophthalein and the bromsulphalein tests, although the latter possibly showed slightly greater changes. With the development of jaundice, there was an increase in the degree of retention of dye. Treatment in this group and in the presence or absence of ascites apparently was without effect on the excretion of dye. The tolerance to fructose was normal in the two cases studied. There was no increase in the bile acids in the blood. The laboratory studies serve further to emphasize the permanent and irremediable nature of the injury to the liver in these cases of cirrhosis.

#### THE HEPATIC COMPLICATIONS OF TREATMENT FOR SYPHILIS POSTARSPHENAMINE JAUNDICE

The complications that develop in the liver during or shortly after a course of antisyphilitic treatment are disturbing and may be serious. There has been considerable discussion as to whether these reactions, particularly the jaundice, were the result of the toxic effects of arsphenamine, of mercury and iodides or of a secondary infectious agent. Possibly, too, a liver injured by syphilis or arsphenamine may



be unduly susceptible to the effect of the minor infections of everyday life. Without attempting to assume a strongly partisan attitude, we have been impressed with the fact that any of these factors may be at fault and that, in addition to the syphilis, some irrelevant entity, such as cholelithiasis, or carcinoma in the biliary system or adjacent viscera, may be the cause of jaundice in a patient recently treated for syphilis. O'Leary<sup>19</sup> emphasized the fact that the appearance of jaundice in a patient in whom a series of injections of arsphenamine or mercury has recently been completed, presents a problem of differential diagnosis which at times may require a long period of observation before definite conclusions are possible. Inadequate knowledge of the syndrome of early hepatic disease in general, with the inadequacy of the laboratory methods available at this time, and the fact that various factors will produce the same clinical syndrome, are the reasons for the present confusion in regard to this complication of jaundice. As is readily realized, the severity of the symptoms of this complication, for convenience called "post-arsphenamine jaundice," is dependent on the degree of injury to the liver whether from arsenic, mercury, staphylococci, streptococci or syphilis. Table 7 with the accompanying case histories is presented to call attention to the various types of hepatic complications observed following treatment for syphilis and to the diagnostic and prognostic value of the tests of hepatic function in this complication.

CASE 115 (table 7) —The patient came to the clinic in November, 1923, with asymptomatic neurosyphilis. The Kolmer modification of the Wassermann reaction of the blood was reported as strongly positive, graded 44. The Wassermann reaction of the spinal fluid was strongly positive, graded 44, the globulin test (Nonne) was positive, and the fluid contained 7 lymphocytes in each cubic millimeter. The colloidal benzoin reaction was 002 000 033 200 000. Results of a general examination were negative. The patient gave a history of having had an acute syphilitic infection in 1921. Previous to coming to the clinic he had received sixteen intravenous injections of neoarsphenamine, and twenty intramuscular injections of mercury salicylate. He had been taking mercury pills at irregular intervals for the last sixteen months.

Under our direction treatment was started on Nov. 16, 1923, the patient receiving seven intravenous injections of arsphenamine at weekly intervals, for a total dosage of 27 Gm. In addition, three intraspinal treatments were given according to the Swift-Ellis-Ogilvie modification, five intramuscular injections of 1 gram (0.065 Gm.) of mercury bichloride (bichloridol) at weekly intervals and ten intravenous injections of 100 cc. of a 10 per cent solution of sodium iodide. The patient was dismissed from the clinic on Jan. 2, 1924, and was advised to start on a course of forty mercurial inunctions of 50 grains (3.25 Gm.) each. He failed to take the rubs, but reported, February 4, that he was feeling well. About February 15, he complained of nausea, loss of ambition and appetite, malaise and pain in the bones and the muscles. These symptoms persisted until March 15, when jaundice

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19 O'Leary, P. A. Postarsphenamin Jaundice, *M. Clin. North America* 8: 1203, 1925.

appeared. The local physician who was called at this time advised an operation for the removal of gallstones. The operation was postponed for six weeks, during which time the jaundice became more intense, and the patient complained more of nausea, loss of weight and the constitutional symptoms so common in cases of infectious jaundice. Against our advice, the patient was operated on elsewhere for cholelithiasis, the diagnosis was based on the persistent painless jaundice. Gallstones were not found, the liver was reported to be somewhat enlarged and congested. Convalescence was somewhat protracted, and the patient remained in the hospital eight weeks, during which time the jaundice did not show a tendency to diminish.

The patient returned to the clinic, June 15, still slightly jaundiced. There was a small amount of free fluid in the abdomen, and slight edema of the ankles, the stools were still clay-colored, and the urine gave a positive reaction for bile. The wound had healed, leaving a small ventral hernia. The reaction of the blood by the Kolmer test still was reported as strongly positive. The serum bilirubin value was 3 mg in each 100 cc. In view of the prolonged and protracted course of the jaundice, the patient was given daily intramuscular injections of succinimide of mercury and a 10 per cent solution of sodium iodide intravenously. Within a few days, he reported that he was feeling better, and he continued to improve rapidly.

This case is an example of a mild type of postarsphenamine jaundice which cleared up without leaving discernible injury in the liver. It is our impression that the jaundice was the result of the treatment that was instituted for syphilis, probably the arsphenamine was the cause.

The jaundice was subsiding when the patient was first observed, and the serum bilirubin content soon dropped to normal from the original value of 3 mg. A direct van den Bergh reaction was present at first, but later it became indirect. There was a lag in the response, however, and the direct van den Bergh reaction persisted for a month or more after the serum bilirubin content had dropped to within the usual limits of normal. There was moderate retention of phenoltetrachlorophthalein which persisted for a considerable period after all other evidence of injury to the liver had disappeared. It gradually decreased, and when the patient was last noted in March, 1927, there was a normal response to all tests.

CASE 116 (table 7)—A man, aged 44, came to the clinic in February, 1926. He had a primary lesion followed by a secondary rash about twenty years before. When he was first examined there was no clinical evidence of activity, but the Wassermann reaction of the blood was strongly positive, graded 44, and the spinal fluid gave a positive globulin reaction and a colloidal gold curve indicative of syphilis. He was given a vigorous course of antisyphilitic treatment, and during a period of eighteen months he received eighteen injections of arsphenamine for a total of 8.3 Gm. and forty-two intramuscular injections of succinimide of mercury in  $\frac{1}{6}$  gram (0.0108 Gm.) doses. The last injection of arsphenamine was in February, 1927. The patient was well for a period but returned May 9, because of painless jaundice of four days' duration. He was in good condition apart from the jaundice. The liver and spleen were not palpable. The serum bilirubin content was 18.7 mg in each 100 cc. He was given daily intravenous injections of

TABLE 7—*Postasphenannic Jaundice*

## PART 1

Case	Date	Age, Years	Sex	Edge of Liver Pal- pable, Graded, Cm 0 to 4	Jaun- dice, Graded, Weeks 0 to 4	Dura- tion of En- larged Spleen, Graded, 0 to 4	Blood Nitrogen Partition, Mg for Each 100 Cc					Serum Bili- rubin, Each 100 Cc	Van- den Bergh Reac- tion	Phenoltetrachlorophthal- en Test						Comment																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
							Non- protein Nitro- gen	Creat- inine	Urea Acid	Amino Acid				Dye in Serum, per Cent		Dye in Urine, Mg		True tose in 100 Mg Test																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																				
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86	7/7/24 7/10/24 7/15/24 7/28/24 8/25/24	46	M	+	3 3 2 1 0	4 4 4 4 0	33 45 47 17	51 55 56	27 30 41	28 25 21	57 61 63 58	176 99 76 13 0.8	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+</

[illegible]

TABLE 7—*Postarsphenamine Jaundice*—Continued

Case	Date	Age, Years	Sex	Edge of Liver Pal- pable, Cm	Jaun- dice, Graded 0 to 4	Dur- ation of Jaun- dice, Weeks	Spleen En- larged	Blood Urea, Mg for Each 100 Cc	Serum Bilirubin, Mg for Each 100 Cc	Van den Berg Reac- tion	Bile Acids, Mg for Each 100 Cc	PART 2 Bromsulphalein Test Dye in Serum, per Cent			Comment
												15	30	60	
												Min	Min	Min	
115	3/17/27	26	M		0		0	18	0.2	0	1.6	2	2	0	Jaundice 3 years before, recovered
116	5/10/27	41	M	0	2	3	0	25	18.7	+	5.1	80	76	72	Latent syphilis, jaundice
	5/13/27				3				19.3	+					Increasing jaundice
	5/16/27				4			21	21.7	+	7.3	76	76	76	Duodenal drainage, no result
	5/18/27				4			18	23.4	+		76	76	76	Maximal jaundice
	5/20/27				1			30	21.2	+		76	76	70	Duodenal drainage, good result
	5/23/27				3			21	18.3	+	5.1	60	60	60	Duodenal drainage, good result
	5/25/27				1			23	13.5	+	1.7	64	60	60	Decreasing jaundice
	5/28/27				2			21	9.9	+	6.5	56	56	10	Dismissed from hospital
	5/31/27				1			22	8.4	+	5.5	56	56	56	Eight months later recovered
	1/10/28				0			29	0.2	0	4.5	8	8	2	
117	11/16/26	48	M	0	2	1	0		15.8	+		80	80	72	Latent syphilis, jaundice
	11/18/26				4			38	21.4	+		64	60	60	Increasing jaundice
	11/21/26				1			10	17.6	+	6.4	80	72	72	
	11/25/26				3				15.6	+		80	75	75	
	11/28/26				4			12	18.7	+	5.5	82	80	80	Condition stationary
	12/2/26				1			20.5	20.5	+		80	80	80	
	12/5/26				1			20.6	20.6	+		80	80	80	Decreasing jaundice
	12/9/26				3			16.5	16.5	+	5.1	90	90	80	
	12/12/26				3			9.0	9.0	+		80	80	75	Dismissed from hospital
	12/11/26				2			11.1	11.1	+		80	80	75	
118	7/21/28	41	M	1	1	1	0		31.8	+		96	96	80	Latent syphilis, jaundice
	7/25/28				3			35	19.0	+		96	96	80	Decreasing jaundice with duodenal drainage
	7/30/28				2				13.6	+					
	8/9/28				1			27	2.8	+		34	16	16	Recovering
119	2/1/28	45	M		3	2			17.3	+	7.4	72	60	60	Neurosyphilis, jaundice
	2/15/28				1			30	2.0	+	4.9	20	8	8	Recovering
120	1/22/27	56	M		3	1		18	5.0	+	7.8	100	66	66	Neurosyphilis, jaundice
	3/2/27				0			16	1.3	+	1.7	6	2	2	Recovery

No.	Date	Age	Sex	Temp	Pulse	B.P.	Weight	Height	Condition
121	7/27/27 8/3/27 8/11/27 8/19/27 9/6/27 1/31/28 8/30/28	48	M	3	2	1	0	107 221 147 143 144 18 20	+ + + + + 0 0
122	3/20/28 4/4/28 4/11/28 6/1/28	42	M	+	1	1		67 78 24 0.2	+ + + ±
123	5/1/27 5/6/27	25	M		2			12 150	+ +
124	4/2/27 4/4/27 4/6/27	47	M	0	2	1		33 31 27	+ + +
125	5/25/28 6/4/28 6/9/28 7/9/28	39	M	0	2	4	0	53 39 17 26	+ + + +
126	1/12/28 1/24/28 2/2/28	50	M	+	2	4	0	18 17 14	+ + +
127	2/11/28 2/15/28 2/21/28 2/23/28 3/9/28	49	M					61 37 17 45 35	+ + + + ±
128	8/2/27	41	M	0	1		0	62	+
129	7/1/26	36	M	0	2	4		54	+
130	8/7/26	32	M	1	2	4			+
131	12/7/25	52	M	3	1	12	0	22	+
132	4/15/25	40	M	0	2	4	0	7	+
133	2/1/27	29	M		0		0	30	0

sodium thiosulphate with duodenal drainage on alternate days. There was little change the first week. The jaundice deepened slightly, and the serum bilirubin increased to 23.4 mg. Only a small amount of bile-stained fluid was obtained by duodenal drainage at this time.<sup>20</sup> The quantity of material obtained gradually increased, and a good flow of bile was secured at the last three drainages. The jaundice began to disappear at that time, and thereafter recovery was uninterrupted. The patient was only slightly jaundiced when he was dismissed from observation on May 31, and he was entirely well when last seen in January, 1928.

This case, clinically, was one of mild postarsphenamine jaundice with complete recovery. The laboratory studies were of interest because it was possible to follow the changes during both the periods of development and of recession of the jaundice. This curve was accurately pictured by the changes in the serum bilirubin. The case was a good demonstration of the value of determining the serum bilirubin content in following the course of a case of jaundice, for the changes were much more clear cut than those in the skin or mucous membranes. A direct van den Bergh reaction was obtained during the course of the jaundice. There was no change in the bile acid content of the blood. There was marked retention of bromsulphalein during the period of jaundice. The degree of dye retention decreased slowly, but persisted for a considerable period after the disappearance of the bilirubinemia. When the patient was last examined in January, 1928, normal readings were obtained with all tests.

CASE 89 (table 7) —A man, aged 60, came to the clinic in May, 1924, when he was found to have parenchymatous and meningeal neurosyphilis. He was given six intravenous injections of arsphenamine for a total of 22 Gm. in conjunction with thirty intramuscular injections of succinimide of mercury and twenty-seven intravenous injections of sodium iodide. This course of treatment was completed about the middle of July, and the patient was sent home with directions to take mercurial inunctions. He returned to our care September 17 because of painless jaundice of two weeks' duration. The serum bilirubin content at that time was 5.6 mg. in each 100 cc. The jaundice, which was associated with light-colored stools and dark urine, gradually progressed. He had lost his appetite, and experienced a marked sense of fatigue and exhaustion, and severe pains in the leg and arm, associated with slight paresthesia of the lower extremities.

Duodenal lavage was unsatisfactory. The increase in the degree of jaundice, and the associated prostration and evidences of toxicity, led us to believe that the patient had toxic hepatitis. As is customary in these cases, there was great irritability of the kidney. The patient remained in the hospital approximately three months and received twenty-one additional injections of succinimide of mercury. Peripheral neuritis was extremely troublesome, and cord bladder necessitated daily irrigation during this time. The jaundice persisted for four months but finally cleared up completely. At the time of dismissal of this patient, a diagnosis was made of toxic hepatitis due either to syphilis or to arsenic. It was approximately a year before the neuritis and the edema of the extremities disappeared, and the patient again began to feel well.

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20 Wilhelm, L. F. X. Duodenal Lavage in the Treatment of Jaundice Complicating the Treatment for Syphilis, *Arch. Dermat. & Syph.* **10**: 499 (Oct.) 1924.

This case was of particular interest because it was possible to follow the changes during the development of jaundice. The serum bilirubin increased progressively from 5.6 to 20 mg in each 100 cc during this period. A maximal degree of dye retention was attained early, and there was relatively little further increase. It was not possible to follow the curve of recovery, but six weeks later the bilirubin and phenoltetrachlorophthalein readings had returned to normal, although the direct van den Bergh reaction persisted.

### ICTERUS GRAVIS

Acute yellow atrophy or icterus gravis may develop as a result of many conditions. Taken by itself it is not characteristic of syphilis, although it occasionally is syphilitic in origin. Many of the reported cases have been described in association with acute secondary syphilis. There is no sharp line of distinction, other than the acuteness and severity, between this condition and the acute syphilitic hepatitis previously described. Similarly, the hepatic injury producing arsphenamine

TABLE 8 (case 134) —*Illustrative Case of Acute Yellow Atrophy*

Date	Blood Urea, Mg for Each 100 Cc	Blood Creatinine, Mg for Each 100 Cc	Phenoltetrachlorophthalein Test Dye in Serum, per Cent		
			15 Minutes	30 Minutes	60 Minutes
9/14/23	184	3.8	34	30	24

jaundice usually is of moderate severity, and the patient readily recovers. In some cases, however, there is an overwhelming injury to the hepatic parenchyma. Such cases may well be classified as acute yellow atrophy. The history of an illustrative case follows.

CASE 134 (table 8) —A man, aged 38, came to the clinic in January, 1923, because of jaundice associated with weakness and malaise. The jaundice had been present about ten days at the time of his admission, also, the lassitude and the loss of appetite had been noted for about two weeks. The stools were clay-colored. The patient had had a definite dull pain in the hepatic region for several weeks preceding the onset of the jaundice. On examination, the Wassermann reaction of the blood was found to be strongly positive, and he gave a definite history of syphilis of twenty years' duration. The liver and the spleen were both greatly enlarged, extending almost to the umbilicus. Antisyphilitic treatment was started, using mercury with chalk by mouth and small doses of potassium iodide. Abdominal pain, which increased steadily for a period of several weeks, necessitated the discontinuance of all treatment. Following this, there was gradual recession in the jaundice and apparent improvement in the patient's general condition. One month after the mercury by mouth had been started, the patient received his first small injection of neoarsphenamine, 0.2 Gm, and in eight days the same dose was repeated. He was sent home the latter part of March somewhat improved.

The patient returned to the clinic in August, however, markedly jaundiced. He said that he had been free from jaundice during April and May but that it



had returned the first of July. Since then he had become progressively worse. It is to be noted that while at home he had been given a series of injections of arsphenamine shortly before the recurrence of the jaundice. He was readmitted to the hospital on Aug. 14, 1923. At that time he was markedly jaundiced, and the liver and spleen were enlarged. The Wassermann reaction of the blood was still strongly positive, graded 44. The urine contained much bile and a moderate amount of albumin, but the blood urea content was 16 mg. in each 100 cc. It was felt at this time that he was showing evidence of a Herxheimer effect in syphilitic hepatitis and splenitis. The routine therapeutic measures were unavailing, and his condition became rapidly worse. Edema of the legs and abdominal ascites developed, and paracentesis by which 1,600 cc. was obtained was done on September 3. The fluid recurred rapidly so that it was impossible to follow changes in the size of the liver which, however, seemed to decrease somewhat. Later there was profuse oozing of blood from the mouth and nose, and still later from the bowel, while the blood urea content rose from 26 to 184. The patient was profoundly toxic the greater portion of the time. Later he became stuporous and was in a state of coma during the last few days of his life. He died on September 15.

Postmortem examination revealed destructive hepatitis and splenitis. The liver weighed 978 Gm. and the spleen, 546 Gm., and the pathologist considered the condition of both to be syphilitic. There was also acute diffuse nephritis.

Laboratory studies were made the day before death. The serum bilirubin was elevated, but a quantitative estimation was not made. A direct van den Bergh reaction was present, and there was marked retention of phenoltetrachlorophthalein. The most striking change was the terminal rise in the blood urea content during the last week of life.

Stadie and Van Slyke<sup>21</sup> and others reported cases of acute yellow atrophy in which there was increase in the amino-acid content of the blood but in which the urea content was normal. The same content of the blood in jaundice is almost pathognomonic for acute yellow atrophy, but we wish to emphasize the fact that there are many cases of icterus gravis in which this particular type of disturbance in the chemical composition of the blood does not occur. The case cited is an example.

#### HEPATIC RECURRENCE AND HERXHEIMER EFFECT IN THE LIVER

Syphilologists have recognized since the advent of arsphenamine two therapeutic effects: the Herxheimer reaction, and the recidive or "recurrence." An outstanding example of the Herxheimer reaction, or therapeutic shock, is observed clinically following the administration of a dose of arsphenamine to a patient with an acute syphilitic roseola. Within twenty-four hours following the injection there is marked accentuation of the cutaneous syphilid, and as a rule there are constitutional signs such as fever and malaise. The clinical evidence of recur-

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21 Stadie, W. C., and Van Slyke, D. D. The Effect of Acute Yellow Atrophy on Metabolism and on the Composition of the Liver, *Arch. Int. Med.* 25: 693 (June) 1920.

ence is most readily observed in patients with acute syphilis who are inadequately treated. One or two injections of arsphenamine, not accompanied by mercury or bismuth, frequently result in the reappearance of the active syphilitic lesions. The same process may take place in the liver, and the following case report is offered as an example of diffuse syphilitic hepatitis or a "hepato-recurrence" which developed in a patient who was inadequately treated for acute syphilis.

CASE 135 (table 9)—A patient, aged 37, had had a penile chancre in June, 1926. He received three intravenous injections of arsphenamine at five day intervals at that time but did not receive mercury. Five days after the last injection he became jaundiced. This jaundice persisted, although it varied somewhat in intensity from day to day. The stools were clay-colored, and pruritus was

TABLE 9 (case 135)—*Progress in an Illustrative Case of Hepato-Recurrence and Heilmeyer Effect in the Liver*

Date	Blood Urea, Mg for Each 100 Cc	Serum Bilirubin, Mg for Each 100 Cc	Van den Bergh Direct Reaction	Bile Acids, Mg for Each 100 Cc of Blood	Bromsulphalein Test Dye in Serum, per Cent		
					15 Minutes	30 Minutes	60 Minutes
1/31/27		21.4	+				
2/14/27	36	35.0	+	11.5		72	40
2/17/27	39	31.6	+	11.0		72	40
2/19/27		27.3	+				
2/21/27		25.9	+				
2/23/27		22.4	+				
2/24/27	22	27.8	+			72	60
2/26/27		20.0	+				
2/28/27	32	14.3	+	7.5		72	72
3/ 2/27	50	14.2	+	6.8		68	60
3/ 4/27		10.2	+				
3/ 7/27		10.4	+			72	68
3/11/27		9.1	+	3.9		72	40
3/14/27	27	8.5	+			72	40
3/17/27	18	6.2	+	5.3		72	40
3/21/27	32	5.3	+			60	44
3/24/27	19	5.9	+	3.8		72	64
5/27/27		0.5	0			12	12

marked. There was no gastro-intestinal disturbance, but he lost 35 pounds (15.9 Kg) in weight. He was admitted to the clinic on Jan. 30, 1927, five months after the appearance of the jaundice. He was moderately icteric, the serum bilirubin content was 21.4 mg in each 100 cc. The edge of the liver was palpable below the costal margin. The Kolmer modification of the Wassermann reaction performed on the blood was negative, but the reaction to the Kahn test was positive.

A moderate amount of bile-stained fluid was obtained on duodenal drainage but the jaundice persisted, the serum bilirubin content fluctuating between 22.4 and 35.0 mg. The patient was given dextrose intravenously for two weeks in addition to the lavages, but without improvement. On February 18, the daily intramuscular injection of succinimide of mercury in 1/6 grain (0.0108 Gm) doses was started. This was supplemented by potassium iodide. He made a steady and uneventful convalescence under this regimen and was dismissed from the hospital on March 22. He was still slightly jaundiced, and the serum bilirubin content was 5.3 mg at that time. Two months later the jaundice had completely disappeared, and the serum bilirubin content was 0.5 mg. The edge of the liver was just palpable. He has remained well since then.

The laboratory studies in this case extend over the major portion of time during which the patient was suffering from an attack of jaundice. There was an initial rise in the serum bilirubin from 21.4 to 35.0 mg in each 100 cc during the development of the jaundice. The bilirubin content in the blood gradually subsided during the period of recovery and had fallen to 5.9 mg when the patient was dismissed on March 24. A direct van den Bergh reaction was obtained during this period. When the patient was seen two months later the serum bilirubin was normal, and the van den Bergh reaction was indirect. The Pettenkofer test showed an increase in the bile acids in the blood at the height of the jaundice. This rapidly disappeared as the clinical condition improved. The bromsulphalein test, on the other hand, showed a maximal retention of dye when the patient first was seen, and this persisted throughout his stay in the hospital. When last seen he still showed moderate retention of bromsulphalein. Unfortunately, it was not possible to examine him at a later date to determine whether there was an eventual return to normal. This case again is an illustration of the value of the determination of the serum bilirubin content in following the course of a case of jaundice.

#### TREATMENT CIRRHOSIS

We have stressed the danger of too vigorous therapeutic measures in the presence of hepatic syphilis. Arsphenamine in particular should be used with caution. This is particularly true because of the insidious character of the injury to the liver produced by arsenic. Much evidence has been accumulated to show that considerable destruction of hepatic tissue may take place without there being any accompanying jaundice or other recognizable clinical symptoms. Fibrous tissue proliferation follows, and with repeated hepatic injury cirrhosis develops. O'Leary, Snell and Bannick<sup>22</sup> reported two cases of portal cirrhosis apparently resulting from the long-continued use of inorganic arsenic as the solution of potassium arsenite. We present the history of a case in which it seemingly followed the use of arsphenamine. This patient, as far as could be judged, was free from syphilis so that the cirrhosis is most readily ascribed to the action of arsphenamine.

CASE 136 (table 10).—The patient first came to the clinic in 1916, when he complained of numbness in the right arm and shoulder. Neurologic examination suggested the possibility of syphilis, and it apparently was confirmed at that time by a weakly positive Wassermann reaction of the blood. During the next five years, he received a series of eighteen intravenous injections of arsphenamine for a total of 7.9 Gm, 200 mercurial injections and approximately thirty-six intra-

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<sup>22</sup> O'Leary, P. A., Snell, A. M., and Bannick, E. G. Portal Cirrhosis Associated with Chronic Inorganic Arsenical Poisoning. Report of Two Cases, *J. A. M. A.* **90** 1856 (June 9) 1928.

muscular injections of succinimide of mercury. The patient was always greatly concerned about the syphilis, and although repeated examinations of the spinal fluid and blood tests following the original course of treatment were all negative, he took further treatment from time to time from other physicians, against our advice. He was seen almost annually, but no further evidence of syphilis was obtained.

In May, 1926, the patient began to have some abdominal pain and enlargement of the abdomen. Walking or jarring materially aggravated the discomfort. Ten days after the onset of this abdominal discomfort, it was noted that he had fluid in the abdomen. He returned to the clinic on May 14, 1926. The skin had a subicteric tint, and there was moderate abdominal distention. The liver and spleen were not palpable. The serum bilirubin content was 4.4 mg in each 100 cc. He was treated with diuretics in the form of ammonium chloride and merbaphen with marked success. At the time of his dismissal, the latter part of June, he had lost 36 pounds (16.3 Kg) and was entirely free from ascites. The liver and spleen were just palpable at the costal margin. He remained well at home but returned to the clinic in August of the same year, for reexamination. There was

TABLE 10 (case 136)—*Progress in an Illustrative Case of Treatment of Cirrhosis, in a Nonsyphilitic Patient*

Date	Blood Urea, Mg for Each 100 Cc	Serum Bilirubin, Mg for Each 100 Cc	Van den Bergh Direct Reaction	Bile Acids, Mg for Each 100 Cc of Blood	Bromsulphalein Test, Dye in Serum, per Cent		
					15 Minutes	30 Minutes	60 Minutes
5/17/23	21	4.4	+	4.4	100	72	54
5/24/23	49	2.8	+		75	54	36
6/ 8/26	29	3.2	+		90	82	54
6/15/26	32	2.7	+				
8/28/26	23	2.4	+			40	15

no evidence of jaundice, the spleen was definitely palpable and the edge of the liver, smooth and firm, could be felt across the right costal border. Ascites was not demonstrated. The serum bilirubin content was 2.4 mg.

The patient was well for a time but returned in October and was admitted in a state of collapse. He died in about twelve hours from a ruptured esophageal varix. Postmortem examination showed a cirrhotic liver considerably reduced in size and a spleen which was four times its normal size. The ruptured esophageal varix, with evidence of gastro-intestinal hemorrhage, was readily demonstrated.

A series of five readings was made on this patient during the three months period between May 17 and Aug 28, 1926. Slight bilirubinemia, a direct van den Bergh reaction and marked retention of dye were uniformly present. These observations are identical with those in the cases of syphilitic cirrhosis previously discussed, and in the cases of portal cirrhosis which we have previously reported.

A history of alcoholism was not present in this case, and the pathologists could not find anything at necropsy to indicate that the hepatic cirrhosis was of syphilitic origin, although a stain for spirochetes was not made. Clinical data elicited during the long period of observation were not of help in arriving at a decision as to the cause of the cirrhosis.

We believe, however, that the use of arsphenamine must be considered an etiologic factor and that this is a true case of treatment cirrhosis in a nonsyphilitic patient

#### JAUNDICE ASSOCIATED WITH MALARIA INOCULATION

The introduction by Wagner-Jauregg of inoculation with malaria as a method of treating neurosyphilis marks an undoubted advance in the treatment for syphilis. O'Leary<sup>23</sup> recently reported in detail his clinical experience with this treatment. Of the 400 patients treated by this method, jaundice of varying degree was observed in about 6 per cent. This is of particular interest, for involvement of the liver in malaria has been recognized since the time of Hippocrates. Cirrhosis is the most common condition of the liver in chronic malaria. This, for the most part, is associated with destruction of erythrocytes and usually is spoken of as belonging to the group of types of pigment cirrhosis rather than to the usual type of portal cirrhosis, although Hance<sup>24</sup> thought it should be classified in the latter group. At the same time, it must be kept in mind that some authorities, as MacCallum,<sup>25</sup> have not considered the relationship of malaria and hepatic cirrhosis as wholly established. Jaundice occasionally is seen in malaria, but it must be admitted that the so-called "bilious" form of malaria is one of the rarer manifestations of that disease.

The etiology of the icterus which accompanies the treatment for neurosyphilis by malaria is difficult to establish. The same situation exists here as is found in the so-called postarsphenamine jaundice. It is recognized that direct action of malaria on the liver, activation of syphilitic hepatitis or some other secondary infectious agent may be at fault. For the present, this must remain an open question. Herewith are the history and results of laboratory examination in an illustrative case.

CASE 137 (table 11) —A dentist, aged 34, first came to the clinic in June, 1925, because of an early case of syphilis of the central nervous system. He had been treated with arsphenamine by his local physician, and when he was examined at the clinic the Wassermann reaction of the blood was negative but that of the spinal fluid was positive. During the next eighteen months he had two further courses of arsphenamine, supplemented by a course of intraspinal treatment according to the Swift-Ellis-Ogilvie technic without a change in the reaction of the spinal fluid.

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23 O'Leary, P. A. Treatment of Neurosyphilis by Malaria. Serologic Results and a Comparison with Treatment by Typhoid Vaccine, *J. A. M. A.* **91** 543 (Aug. 25) 1928.

24 Hance, J. B. On Malaria as an Independent Etiological Factor in Portal Cirrhosis, *Guy's Hosp. Rep.* **78** 379, 1928.

25 MacCallum, W. G. A Text-Book of Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1924, p. 1162.

TABLE 11—Jaundice Associated with Malaria Inoculation

Case	Date	Age, Years	Sex	Degree of Liver Pal- pable, Graded Cm	Jaun- dice, 0 to 1	Spleen En- larged	Hemo- globin Con- tent	Rythro- cytes, Millions	Leuko- cytes	Blood Urea, Mg per 100 Cc	Blood Uric Acid, Mg per 100 Cc	Serum Bili- rubin, Mg per 100 Cc	Van- den Berg Direct React	Bile Acids, Mg per 100 Cc	Bromsulphalein Test, Dye in Serum, per Cent			Comment
															15 Min	30 Min	60 Min	
137	12/9/26 12/21/23	35	M	0 0	0 2	0 1	77 55	1.68 2.95	8,000 7,800	18 72	2.7 5.7	6.6	0 1	0		36	36	Neurosyphilis, malaria inoculation After 10 chills
138	1/25/27 1/5/27 1/7/27 1/11/27 1/18/27	50	M	0 0 0 0 0	0 1 2 1 1	0 0 0 0 0	73 60 60 60 55	1.11 1.57 1.48 1.40	7,100 7,000 7,400 8,600	30 39 21 17 25	2.0 2.4 2.5 2.2	6.8 8.2 1.1 3.3	1 1 1 1	5.6 5.1 1.7 3.6		60 75 60 60 10	40 60 60 36	Neurosyphilis, malaria inoculation After 1 chills Quinine given Recovering
139	1/13/27 1/21/27	12	M	0 0	0 1	0 0	75 55	1.36 1.21	7,600 2,900	16 70	2.9 5.3	3.0	1	1		30	20	Neurosyphilis, malaria inoculation After 9 chills
140	7/15/26 7/25/26 2/23/27	15	M	0 2 0	0 2 0	0 1 0	72	1.59	1,400	36	3.6	23.1 0.6	1 0	5.6 6.6		80 1	0	Neurosyphilis, malaria inoculation After 1 chills Seven months later, recovered
141	5/20/27 6/1/27 6/20/27	36	M	0 0 0	0 1 1	0 0 0	73 70 50	1.60 1.31 2.70	6,800 6,600 5,000	18 28 16	2.1 2.3 3.2	3.0	1	5.5		21	20	Neurosyphilis, malaria inoculation After 2 chills After 10 chills
142	1/21/28 5/5/28	29	F	0 0	0 1	0 1	51 50	1.14 2.77	5,000 4,000	20 40	3.1 4.9	1.7	1			30	29	Neurosyphilis, malaria inoculation After 1 chills

Inoculation with malaria was given on Dec 2, 1926. The first chill occurred four days later. Quotidian chills occurred during the next ten days. There was slight conjunctival icterus on December 14, which progressively increased. Enlargement of the spleen could first be demonstrated on December 20. The patient had ten chills by December 22. There was moderate jaundice, and the spleen was readily palpable. Quinine was then administered, and there was a cessation of the chills and rapid disappearance of other symptoms. Three days later the spleen was no longer palpable, and the jaundice had markedly decreased.

Anemia developed rapidly with a marked fall in both the hemoglobin content and the erythrocyte counts, but the leukocyte count was unchanged. The urinary output was more than 1,000 cc daily, but the blood urea content rose progressively from 18 to 72 mg in each 100 cc, and the uric acid from 27 to 57 mg in each 100 cc. Marked jaundice developed with a serum bilirubin content of 66 mg in each 100 cc and a direct van den Bergh reaction. There was retention of bromsulphalein as well.

The changes observed in this patient are characteristic and serve to illustrate those seen in the group as a whole. There are several possible explanations of the changes in the blood. The production of anemia, with the associated appearance of jaundice, suggests a hemolytic crisis in consequence of a destruction of erythrocytes by plasmodial invasion. To that extent the changes may be compared with the similar hemolytic crisis produced by the therapeutic administration of phenylhydrazine in cases of polycythemia vera. The changes in the latter have been reported by Greene and Conner<sup>26</sup> and more recently by Huffman<sup>27</sup>. Huffman found that during therapeutic use of phenylhydrazine there was rapid production of anemia. As the hemoglobin of the destroyed erythrocytes was broken down, the pigment moiety was excreted in the bile as bilirubin, and the protein fractions appeared in the urine as urea. Practically all the destroyed blood could be accounted for in this way. Because of the rapidity of blood destruction, the eliminative facilities of the body were temporarily embarrassed. In consequence, there was transitory increase in the blood urea and serum bilirubin, with consequent jaundice. Apart from this there was little metabolic disturbance, and recovery was rapid and complete.

A similar hemolytic crisis will explain many of the changes in the jaundice following inoculation with malaria. The anemia, jaundice, enlargement of the spleen, bilirubinemia and increase in the blood urea may all be explained on this basis. This view is apparently held by Stitt<sup>28</sup>. Simple hemolysis, however, will not explain all the changes

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26 Greene, C. H., and Conner, H. M. Diseases of the Liver. V. A Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System, *Arch. Int. Med.* **38** 167 (Aug.) 1926.

27 Huffman, L. D. Metabolic Studies in the Treatment of Polycythemia Vera with Phenylhydrazine, *Arch. Int. Med.* **39** 656 (May) 1927.

28 Stitt, E. R. The Diagnosis and Treatment of Tropical Diseases, Philadelphia, P. Blakiston's Son & Company, 1929, pp. 33, 34, 45, 48 and 63.

present Hemolytic icterus and the jaundice following treatment with phenylhydrazine are characterized by the presence of an indirect van den Bergh reaction and normal values for the bromsulphalein test. Retention of dye and a direct van den Bergh reaction were uniformly present in the cases of jaundice accompanying malaria. These changes can be taken as direct evidence of some degree of hepatic injury, however slight. Likewise, the increase in the uric acid content of the blood is evidence of injury to the tissues and need not be referred exclusively to renal injury. We believe, therefore, that the jaundice associated with inoculation with malaria is not to be considered as due entirely to destruction of blood but must be classified as a hemohepatogenous type of icterus.

#### LABORATORY DATA

*Fructose Tolerance*—Previous experience with the fructose tolerance test in patients with obstructive jaundice or the various types of hepatitis with jaundice was disappointing in contrast to the results of Isaac,<sup>29</sup> Kleeberg,<sup>30</sup> Tachau<sup>31</sup> and others. The changes observed were not sufficiently marked or specific to be of particular diagnostic value. A group of ten patients was subjected to the test in the present series. Only two positive reactions were obtained. Further study did not seem justified, and the test was discarded.

*Nitrogen Partition of the Blood*—A slight decrease in the blood urea level is found in some of the cases of jaundice observed in this series. The change, however, was always to be explained by reference to the individual case, and usually by the use of diets low in protein and rich in carbohydrate, temporary forcing of the intake of fluids or similar factors. In one case of destructive hepatitis leading to subacute yellow atrophy, the blood urea was normal until just before death, when there was a terminal rise. A similar terminal rise was noted in a case of hepatic gumma and in one of portal cirrhosis. Temporary elevation of the blood urea likewise was noted in the course of several cases of postarsphenamine jaundice, but the administration of large amounts of dextrose and the forcing of fluid in such cases caused a rapid return to normal.

The other nitrogenous constituents of the blood which were studied, the total nonprotein nitrogen, uric acid, creatinine and amino-acid nitrogen did not show characteristic changes.

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29 Isaac, S. Die klinischen Funktionsstörungen der Leber und ihre Diagnose, *Ergebn d inn Med u Kinderh* **27** 423, 1925.

30 Kleeberg, Ludwig. Über Leberfunktionsprüfungen bei Lues, *Med Klin* **2** 1162, 1920.

31 Tachau, P. Untersuchungen über die Funktion der Leber bei Lues, unter besonderer Berücksichtigung des Ikterus syphiliticus praecox und der Leberstörungen durch Salvarsan, *Dermat Ztschr* **32** 305, 1921.



*Bile Pigments*—The value of the serum bilirubin test as a means of following the progress of a case of jaundice is too well recognized to require special emphasis<sup>32</sup> The results in this series are in entire agreement with the observations made in the other varieties of jaundice which have been studied and reported from this clinic The estimation of the serum bilirubin offers a more sensitive index to daily changes in the degree of jaundice than the color of the skin or the amount of bile in the urine The determination of the serum bilirubin content in early cases of toxic hepatitis, or in cases of cirrhosis, has permitted the recognition of latent jaundice before the icterus became manifest clinically Reference should also be made, particularly in postarsphenamine jaundice, to the disparity observed in some cases between the intensity of the jaundice and the clinical symptoms During recovery, the two tend to improve together, but at the height of the disease they do not necessarily correspond This emphasizes the point that a single determination is of less value than a study of the curve of change in the serum bilirubin The degree of bilirubinemia in the cases of postarsphenamine jaundice was entirely comparable with those observed in the acute hepatitis of nonsyphilitic origin, the maximal value was 32.5 mg of bilirubin in each 100 cc Normal values for the serum bilirubin were found in those cases of syphilis in which there was no involvement of the liver and in those of hepatic gumma

A direct van den Bergh reaction was observed in all the cases of marked jaundice of whatever type In ordinary usage, we have not found any advantage in following the various reported subgroups of this reaction The majority of these have been reported as direct in the accompanying tables In cases of postarsphenamine jaundice we have observed that there may be a slight initial increase in the serum bilirubin, while the serum gives an indirect or delayed direct van den Bergh

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32 Chargin, Louis, and Orgel, S. Z. Jaundice in Syphilitic Persons Receiving Arsenical Medication Its Early Detection and Possible Prevention, *Arch Dermat & Syph* **7** 495 (April) 1923 Dixon, H. A., Campbell, W. R., and Hanna, M. I. The Control of Arsphenamine Treatment by Liver Function Tests, *Canad M A J* **16** 551, 1926 Gerrard, W. I. The Recognition of Latent Jaundice During Treatment with Arsenobenzol Compounds, *Brit M J* **2** 224, 1924 Kloeppel, F. W. Lues und Salvarsan in ihrem atologischen Zusammenhang mit Bilirubinämie und Ikterus, *Dermat Ztschr* **37** 137, 1922-1923 Schamberg, J. F., and Brown, Herman. Bilirubin Determinations in the Blood as a Measure of Liver Damage in Treatment with Arsphenamines, *J A M A* **82** 1911 (June 14) 1924 Schneider, Paul. Untersuchungen über den Bilirubingehalt des Blutserums bei Salvarsan-Quecksilberkur, *Dermat Wchnschr* **74** 228, 1922 Strauss, L., and Buerckmann, W. Der Einfluss des Salvarsans auf die Bilirubin-Reaktion im Blutserum bei Lueskranken, zugleich ein Beitrag zur Frage der Salvarsanschädigungen, *Klin Wchnschr* **1** 1407, 1922 Wechselmann and Hohorst, W. Ueber den Einfluss der Salvarsanbehandlung auf den Bilirubingehalt des Blutserums, *Arch f Dermat u Syph* **136** 285, 1921

reaction This changes rapidly, and with further increase in the amount of pigment retained in the blood the reaction becomes direct Similarly, as the jaundice disappears, a direct or delayed direct reaction may be obtained for several days or even for several weeks after the normal level of bilirubin is regained

*Dye Retention*—Phenoltetrachlorophthalein was used to measure the retention of dye in the majority of these cases In the more recent cases bromsulphalein was used instead The results were qualitatively alike with the two dyes Normally they leave the blood at different rates, therefore, the samples of blood must be taken at different times Because of this it is not possible to compare the two dyes directly or to convert readings obtained with one into readings obtained with the other However, we have not observed definite retention of phenoltetrachlorophthalein without likewise finding retention of bromsulphalein Bromsulphalein is somewhat less irritating to the veins than phenoltetrachlorophthalein and so is preferable for repeated use

Retention of these dyes was observed in all cases of hepatitis with jaundice of whatever type<sup>33</sup> The changes again are similar to those found in nonsyphilitic cases The changes in retention of dye are similar to those observed in the serum bilirubin although the return to normal in the retention is greatly delayed In the majority of the cases of toxic hepatitis or postarsphenamine jaundice, the abnormal retention of dye completely disappeared after recovery, but a slight degree of retention occasionally persisted for a considerable period following recovery and the return of the bilirubin to normal

The results in general were similar in the various forms of syphilitic hepatitis In case 6 (table 5), the phenoltetrachlorophthalein reading returned to normal with the clearing up of the initial hepatic lesion With further progress and the apparent development of cirrhotic changes, abnormal retention of dye again appeared

The cases of gumma were variable The majority showed slight degrees of abnormal retention of dye The readings obtained in the

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33 Broun, G O Toxíc Hepatitis Following Salvarsan Administration, *M Clin North America* **7** 989, 1923 Epstein, N N, and Rauschkolb, J E The Rose Bengal Test for Liver Function with Particular Reference to Its Use in the Therapy of Syphilis, *Arch Dermat & Syph* **14** 122 (Aug) 1926 Greenbaum, S S, and Brown, Herman The Phenoltetrachlorophthalein Liver Test in Cases of Acute and Chronic Syphilis Under Treatment and in Various Skin Diseases, *J A M A* **82** 88 (Jan 12) 1924 Piersol, G M, and Bockus, H L Comparative Studies in Liver Function by Some of the Later Methods, *J A M A* **83** 1043 (Oct 4) 1924 Piersol, G M, and Rothman, M M Practical Value of Liver Function Tests A Comparative Study, *J A M A* **91** 1768 (Dec 8) 1928 Rosenthal, S M The Phenoltetrachlorophthalein Test for Hepatic Function Recent Studies with the Author's Method, *J A M A* **83** 1049 (Oct 4) 1924

different cases varied considerably, depending, perhaps, on both the extent and the severity of the process in the liver. The cases of cirrhosis, on the other hand, were more uniform, practically all showed the presence of a moderate degree of retention. The results of the phenoltetrachlorophthalein and bromsulphalein tests, in such cases, are of greater diagnostic value, for in these, retention of dye occurs without there being a coincident elevation of the serum bilirubin.

*The Bile Acids*—The study of the bile acid content of the blood by means of the Pettenkofer test was without diagnostic import in this series of cases. In a few cases of syphilitic hepatitis with jaundice, or of postarsphenamine jaundice, there was an increase in bile acids. The increase in the bile acids apparently is transitory and is confined to the acute stage of the disease. The normal level of bile acids is regained much sooner than is that of the serum bilirubin and sooner, also, than the retention of dye becomes normal. The changes in the bile acids, therefore, are similar in character to those found by Snell, Greene and Rowntree<sup>34</sup> in experimental obstructive jaundice. In all but these few cases, the values for the bile acid content of the blood, as given by the Pettenkofer test, were within the usual limits of normal.

#### COMMENT

"Syphilis, the great imitator, is perhaps never seen in a more advantageous rôle, as such, than in hepatic disease"<sup>15</sup> The present group of cases well illustrates the applicability of this statement. The different clinical pictures cited, as well as the various accompanying laboratory data, have their counterparts in nonsyphilitic disease. In consequence it is necessary, in a discussion of the hepatic complications of syphilis, to speak not in general terms but in specific terms, not of syphilis of the liver, but of a particular form of hepatic syphilis. Differential diagnosis is difficult, and may require the use of all available information, whether from the history, general examination or laboratory examinations. Such information is essential both for prognosis and for the institution of rational treatment.

This is well illustrated by a comparison of acute syphilitic hepatitis accompanied by jaundice with postarsphenamine jaundice. The differentiation is to be made wholly on the basis of the history and the clinical data. Acute syphilitic hepatitis with jaundice develops independently of treatment and appears in association with, or shortly following, the appearance of the secondary manifestations of acute syphilis. When it is of a mild form, acute hepatitis responds to antisymphilitic measures,

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34 Snell, A. M., Greene, C. H., and Rowntree, L. G. Disease of the Liver VII. Further Studies in Experimental Obstructive Jaundice, *Arch. Int. Med.* 40: 471 (Oct.) 1927.

but when it is severe it may progress to acute yellow atrophy and death. Postarsphenamine jaundice, on the other hand, develops in a patient who previously has received treatment. The course of the mild case is usually uneventful, and as Wilhelm<sup>21</sup> showed, it responds readily to therapeutic procedures. The severe forms, on the other hand, may go on to acute yellow atrophy, or, if the injury is less acute, a portal type of cirrhosis may be produced. Once the jaundice has developed, the clinical symptoms and the degree of apparent intoxication of the patient are alike in the two types. Then the differences are more of degree, than of kind, and so are not characteristic. In consequence, the differential diagnosis must be made largely on the basis of the history and collateral information. The confusion of postarsphenamine jaundice with the ordinary nonspecific infectious hepatitis likewise has been pointed out, among others, by Stokes, Ruedemann and Lemon<sup>35</sup>.

The changes in the functional tests in these forms of acute hepatitis are indistinguishable. The most useful of the criteria available for showing the development and intensity of hepatitis following the administration of arsphenamine is the determination of bilirubin. An increase in the serum bilirubin precedes the first sign of incipient or developing icterus, a point to which numerous authors have called attention. Similarly, decrease in the serum pigment and return of the bilirubin to the normal level precedes the disappearance of the icterus in the skin and mucous membranes. The dyes, whether phenoltetrachlorophthalein or biomsulphalein, are retained in a fashion similar to the retention of bilirubin, although the fluctuations with the course of the disease are not so marked, and the return to normal is not so rapid as in the case of the bilirubin. Because of the greater sensitivity to daily fluctuations and ease of the procedure, determination of the bilirubin content is somewhat more satisfactory for routine use in these cases.

The diffuse hepatitis of late syphilis is to be classified clinically as a subacute or chronic process, by contrast with the acute process seen in the acute hepatitis of secondary syphilis or in postarsphenamine jaundice. The condition in the majority of these cases is apparently remediable, and the patients recover more or less completely under antisiphilitic treatment. This is not always so, however, for with sufficient injury there is permanent injury to the liver. Biliary cirrhosis results, and this must be looked on as the end-stage of the response of the liver to chronic injury. The possibility of the development of such a cirrhosis emphasizes the importance of prolonged observation of these patients, even after apparent clinical cure, before a decision is reached regarding the extent of residual injury to the liver.

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35 Stokes, J. H., Ruedemann, Rudolph, Jr., and Lemon, W. S. Epidemic Infectious Jaundice and Its Relation to the Therapy of Syphilis, *Arch. Int. Med.* 26: 251 (Nov.) 1920.

Correspondence between the cases of portal cirrhosis in syphilitic and in nonsyphilitic patients also is to be noted. The clinical features and the symptoms, so far as the liver is concerned, are identical in the two groups. The changes in the various tests are alike, and the pathologic picture has no distinguishing features. It is difficult at times, even with the aid of microscopic studies, to determine what part syphilis alone has had in the development of this type of cirrhosis. On the other hand, it generally is accepted that portal cirrhosis represents the end-stage in the response of the liver to injury and represents the combined effect of the processes of degeneration, deposition of fibrous tissue and regeneration. An increasing number of cases has been collected and reported in which such cirrhosis has followed recovery from acute yellow atrophy. As syphilis is capable of producing acute destructive hepatitis of the type of acute yellow atrophy it is logical to assume that some of these cases of idiopathic portal cirrhosis were syphilitic in origin. Arsenic may produce a similar disturbance, whether given in inorganic form or as arsphenamine. Case 136 apparently is an example of such portal cirrhosis in a nonsyphilitic patient, which emphasizes the need for extreme care in the administration of arsphenamine in the presence of hepatic disease. The permanent and irremediable nature of the changes in the liver in portal cirrhosis emphasizes the importance of preventive rather than curative measures in treatment. In these cases, too, the bromsulphalein and phenoltetrachlorophthalein tests are of diagnostic and prognostic value as an index to the changes in the liver.

The picture of gumma of the liver is unusual in that the symptoms produced, as a rule, are much less distinct than ordinarily would be anticipated from the degree of hepatic involvement. The functional tests, especially the bromsulphalein or phenoltetrachlorophthalein tests, likewise show only minimal changes in the process of outspoken pathologic changes. The condition in gumma emphasizes the limitation in value of the different tests as affected by the type of lesion present. A diffuse lesion affecting the organ as a whole produces changes which are demonstrated readily. A localized lesion, such as a gumma, on the other hand, is limited in extent and the remainder of the organ may be relatively normal. In view of the large reserve in the liver, normal reactions are to be expected.

#### SUMMARY

We are impressed with the varied types of hepatic disease that may be produced by a syphilitic infection, a condition that calls to mind the multiform lesions in the skin produced by the same infection. Consequently, it is necessary to speak not of syphilis of the liver in the general sense but rather of a specific type of hepatic lesion. The chief characteristics of the clinical pictures and the results of laboratory examina-

tions in these different conditions have been discussed. This discussion has emphasized the difficulty of differential diagnosis that frequently is encountered and the importance in making the diagnosis of using all available information, whether from history, general examination, laboratory tests, therapeutic trial or prolonged observation. The indications for the use of the different tests for hepatic function and their limitations have been discussed. These tests give results that are dependent on the extent and nature of the injury to the liver rather than on the specific etiologic agent concerned. For this reason, the probable type and extent of the pathologic process must be considered in interpreting the results of laboratory examination. When due regard is paid to these matters, the various tests of hepatic function have definite value in supplementing other methods of studying the patient.

# OPIUM ADDICTION

## VII A COMPREHENSIVE STUDY OF EFFECTS OF THE SCOPOLAMINE TREATMENT FOR MORPHINE ADDICTION<sup>1</sup>

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AND

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PHILADELPHIA

The routine treatment that we have employed in the Philadelphia General Hospital has been confined chiefly to the scopolamine method. We have made studies of the addicts before treatment was begun and at intervals of from two to four days following the apparent cessation of the withdrawal symptoms, which were universally present while the patients were under the influence of scopolamine. During the latter study period, we encountered all grades of behavior and appearances of illness. We wish to report in this paper comparative studies made while morphine was being administered to supply the needs of the addict and again following the cessation of mental confusion produced by scopolamine. These studies include those of the heart and circulation, physical and chemical properties of the blood, metabolism, temperature, changes in weight, vital capacities, the urine, functional tests of the kidney and liver, and reaction to epinephrine and to atropine.

### METHOD OF TREATMENT

The routine method of treatment, which was carried out in a more or less uniform manner, is as follows. During the first twenty-four hours following admission, the patient is given morphine sulphate hypodermically in sufficient quantities to prevent withdrawal symptoms. If no studies during the administration of morphine are contemplated, he is placed on a liquid diet for this period. At the same time he is given a diastolic dose of mild mercurous chloride or mass of mercury, U S P, followed in eight hours by a saline cathartic. At the end of the twenty-four hour period, scopolamine hydiobromide is given in doses of  $\frac{1}{200}$  grain (0.3 mg) hypodermically at four hour intervals, for three doses. With each dose of scopolamine is given  $\frac{1}{40}$  grain (1 mg) of strychnine.

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<sup>1</sup> Submitted for publication, March 5, 1929.

<sup>2</sup> From the Narcotic Wards of the Philadelphia General Hospital.

\* Expenses of this research were defrayed by the Committee on Drug Addictions, New York City, and the work was carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction in the Narcotic Wards of the Philadelphia General Hospital which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia.

sulphate Following this, the dosage of scopolamine is raised to  $\frac{1}{150}$  grain (0.4 mg) for three doses and then increased to  $\frac{1}{100}$  grain (0.6 mg) accompanied each time with  $\frac{1}{40}$  grain strychnine The total period covered by the administration of scopolamine covers thirty-six hours When the effects of the scopolamine begin to disappear, if withdrawal symptoms are still quite severe, they are combated with large doses of phenobarbital, or frequently a single dose of  $\frac{1}{4}$  grain (16 mg) of morphine sulphate is given Treatment from this time on is purely symptomatic, consisting chiefly of sedatives to promote sleep for three or four days as well as small doses of bicarbonate of soda for any gastric distress Patients are usually discharged at the end of a period of ten days

#### EXPERIMENTAL PROCEDURE

These studies were usually conducted between the first and the fourth day following the disappearance of the mental confusion caused by the scopolamine Practically all of our observations and studies were made during the morning hours while the subject was reclining in bed, not having had breakfast The subjects were requested to recline in bed for a period of one-half hour The figures for the pulse and respiration rates are the averages of a five minute count, and the figures for the blood pressure the average for as many determinations of pressure as could accurately be made in a five minute period Following these observations, the basal metabolic rate and temperature were measured and recorded Krogh's apparatus for recording the basal metabolism was used and checked once a week with a subject whose basal metabolic rate was known to be normal Schneider's test for physical fitness<sup>1</sup> and determinations of vital capacity were usually next in order, followed by the taking of a sample of blood for analysis The addict was then requested to pass a sample of urine, and following this he was subjected to the climb of two flights of stairs, as described by us in a previous paper<sup>2</sup> Studies of the reaction to epinephrine and functional tests were carried out, as a rule, with the subjects reclining in bed The procedure followed in the study of the effect of atropine sulphate on the P-R interval was the same as that described in the paper giving the results obtained during addiction<sup>2</sup>

#### RESULTS

Our results, shown in table 1, indicate that following treatment there was no change in the average pulse rate while the subjects were reclining

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1 Schneider, Edward C A Cardiovascular Rating as a Measure of Physical Fatigue and Efficiency, *J A M A* **74** 1507 (May 29) 1920

2 Light, Arthur B, and Torrance, Edward G Opium Addiction III The Circulation and Respiration of Human Addicts During the Administration of Morphine, *Arch Int Med* **43** 556 (April) 1929



and the average blood pressures while they were reclining and standing, but there was an average increase of 20 beats per minute in the pulse rate while the subjects were standing and an average increase of 3 respirations per minute while they were reclining. Fifteen of the twenty-three cases after treatment showed a rise in the pulse rate while the subjects were standing as compared to the average rate before treatment, in one, the rate remained the same and in four there was a slight decrease.

TABLE 1—*A Comparison of the Circulation and Respiration of Human Opium Addicts Before and After Treatment with Scopolamine*

	Before Treatment	After Treatment
Pulse Rate while Subject Was Reclining		
Number of cases	50	23
Highest	84	96
Lowest	52	50
Average	65	68.5
Pulse Rate while Subject Was Standing		
Number of cases	30	23
Highest	112	134
Lowest	66	76
Average	79	99
Blood Pressure while Subject Was Reclining		
Number of cases	40	24
Highest	138/92	128/84
Lowest	98/62	102/64
Average	117/72	117/74
Blood Pressure while Subject Was Standing		
Number of cases	28	21
Highest	138/80	118/100
Lowest	88/64	90/60
Average	108/74	109/75
Respirations		
Number of cases	43	20
Highest	22	30
Lowest	10	13
Average	18	21

Measurements of the heart made by means of the orthodiagram in nine cases before and after treatment showed an average decrease in the ratio of the transverse diameter of the heart to that of the chest of from 44.4 to 41.2 per cent. The average diameter of the aortic arch remained the same, being 4.8 mm. after treatment and 4.7 mm. when morphine was being administered.

Table 2 contains a summary of the average changes obtained in the blood pressure and the pulse and respiration rates following the staircase climbing test both before and after treatment. Charts 1 and 2 show graphically the average absolute readings obtained. The response to staircase climbing following treatment compared with the results obtained during the administration of morphine shows that the immediate increase in the pulse rate was somewhat less than during the administration of the drug. The increase in the respiratory rate and

failure of the rise in systolic pressure to the height reached during the administration of morphine indicate a slightly poorer response following treatment, if the curves obtained from a series of trained athletes undergoing similar tests are used to show the response of an adequate circulation

Electrocardiographic studies in a series of eight addicts before and after treatment showed no abnormal changes in the conformation of the various waves. There was a slight decrease in the average P-R interval following treatment, namely, from 0.15 to 0.145 second. At the same time, however, the average rate increased following treatment to 85 beats per minute as compared to 75.8 beats during the administration of morphine. The effect of the injection of  $\frac{1}{20}$  gram (3 mg) of atropine sulphate was no different after treatment from that while morphine was

TABLE 2—*A Comparison of the Average Increases of the Pulse, Systolic Pressure and Respiration Rate and Changes in the Diastolic Pressure in Opium Addicts During Administration of Morphine and After Treatment with Scopolamine*

	Number of Cases	Before Treatment						After Treatment					
		1st Read- ing	1st Min	2d Min	3d Min	4th Min	5th Min	1st Read- ing	1st Min	2d Min	3d Min	4th Min	5th Min
Pulse	9	62	37	20	13	11	12	57	34	15	6	4	4
Systolic pressure	9	29	30	25	16	9	1	19	23	19	13	7	3
Diastolic pressure	9	-10	-7	-6	-6	-6	-6	-12	-7	-5	-4	-1	-0
Respirations	9		5	2	1	1	1		9	5	3	2	1

still being administered. In both studies the P-R interval was decreased 0.02 second, the average decrease coming at approximately the same time, namely, 14.5 minutes before and 12 minutes following treatment. The effect of the atropine on the heart rate was unchanged by treatment. In both instances, the percentage of increase of the heart rate was 45, and the average time of the greatest increase 24.7 minutes during the administration of morphine and 22 minutes following the treatment.

Schneider's test of physical fitness showed a decided fall in the average number of points scored following treatment. Seventeen cases studied during the administration of morphine scored an average of 13.3 points, while the average score following treatment was only 6.9 points. Fifteen of the seventeen cases showed this fall in score, one case scoring the same number of points, the two remaining cases showed a rise of two points following treatment.

Vital capacities in eight cases averaged practically the same while the subjects were receiving morphine as compared to the average obtained following the administration of scopolamine, namely, 4.047 cc before treatment and 4.016 cc following treatment.

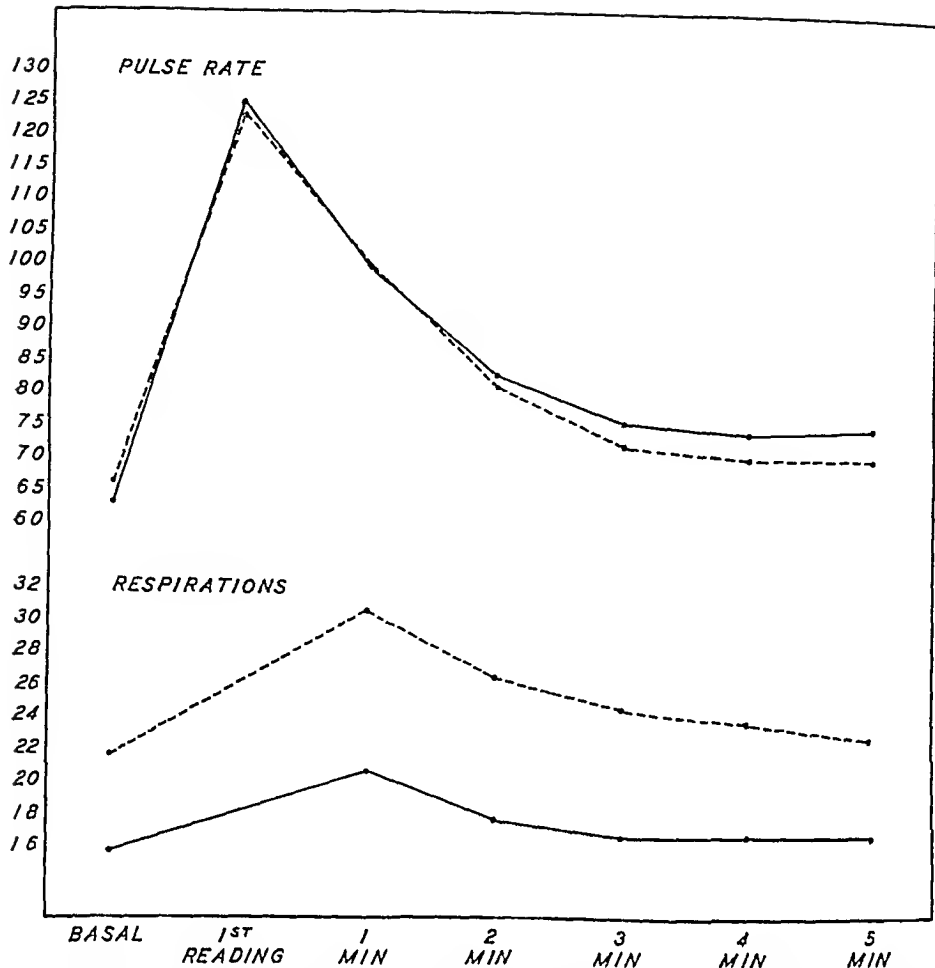


Chart 1—Average changes in the pulse and respiration rates, in response to staircase climbing test in a group of human addicts receiving morphine and following treatment with scopolamine. In this chart and in charts 2 and 3, the solid line indicates before treatment and the broken line, after treatment.

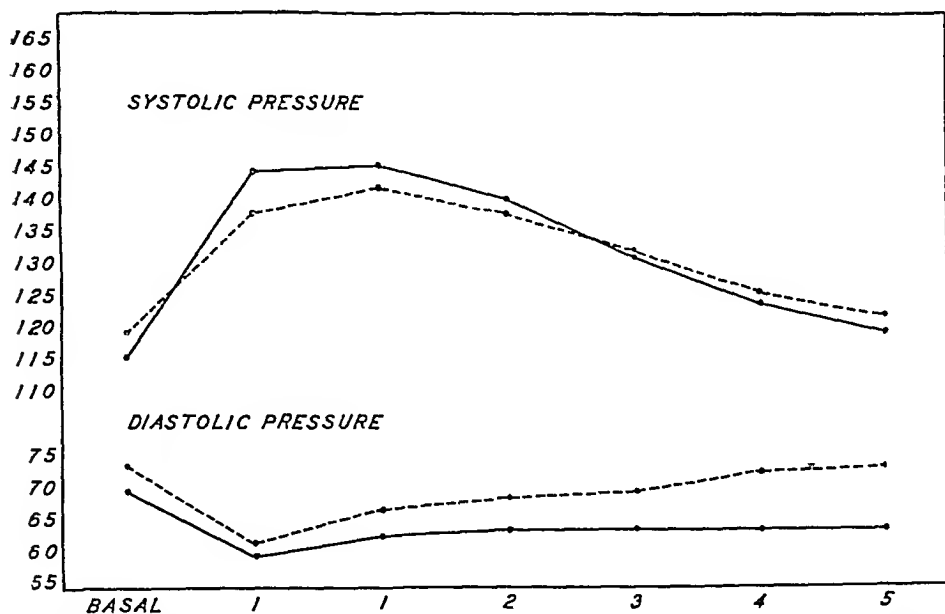


Chart 2—Average changes in the systolic and diastolic blood pressure in response to the staircase climbing test in a group of human addicts receiving morphine and following treatment with scopolamine.

*The Blood*—Results obtained from studies of the blood before and after treatment, given in table 3, show practically no significant changes. The average number of red blood cells has increased slightly, namely, 177,000 per cubic millimeter when compared to the results obtained

TABLE 3—*A Comparison of the Physical and Chemical Properties of the Blood of Human Opium Addicts Before and After Treatment with Scopolamine*

	Hemoglobin, Gm per 100 Cc		Erythrocytes, Number per C Mm		Leukoocytes, Number per C Mm		Polymorpho- nuclears, per Cent	
	Before	After	Before	After	Before	After	Before	After
Number of cases	26	19	29	10	33	10	28	7
Highest	19.4	18.4	4,960	5,100	15,400	16,400	78	80
Lowest	12.0	13.2	3,640	4,395	2,500	4,000	33	45
Average	15.2	15.8	4,533	4,710	9,359	11,166	61	61

	Lympho- cytes, per Cent		Large Mononuclears, per Cent		Eosino- phils, per Cent		Baso- phils, per Cent		Blood Urea Nitrogen, Mg per 100 Cc	
	Before	After	Before	After	Before	After	Before	After	Before	After
Number of cases	28	7	28	7	28	7	28	7	28	16
Highest	63	53	7	7	2	2	3	2	24	20
Lowest	20	19	0	½	0	0	0	0	10	9
Average	34	35	3	3	½	½	1½	½	13.2	14

	Blood Sugar, Mg per 100 Cc		Blood Uric Acid, Mg per 100 Cc		Blood Lactic Acid, Mg per 100 Cc		Blood Cholesterol, Mg per 100 Cc		Blood Sodium Chloride, Mg per 100 Cc	
	Before	After	Before	After	Before	After	Before	After	Before	After
Number of cases	32	16	22	12	6	6	16	18	9	2
Highest	122	166	4.5	4.8	31.1	38.4	250	274	570	560
Lowest	72	80	2.4	2.4	20.1	22.6	158	120	480	490
Average	97	100	3.3	3.4	25.0	31.8	208	198	511	525

	Serum Calcium, Mg per 100 Cc		Serum Phosphate, Mg of Phosphorus per 100 Cc		pH Plasma		Carbon Dioxide Capacity of Plasma, per Cent by Volume	
	Before	After	Before	After	Before	After	Before	After
Number of cases	14	5	11	5	20	10	20	10
Highest	14.4	13.1	3.2	2.8	7.51	7.45	71	63
Lowest	9.8	10.1	2.6	2.2	7.28	7.33	15	48
Average	10.9	11.7	2.8	2.6	7.36	7.41	57.7	52

	Dry Matter of Whole Blood, per Cent		Dry Matter of Plasma, per Cent		Dry Matter of Cells, per Cent		Red Blood Cells, per Cent by Volume	
	Before	After	Before	After	Before	After	Before	After
Number of cases	22	17	15	11	7	8	6	10
Highest	22.7	23.6	10.2	10.4	48.0	41.8	38.7	49.0
Lowest	15.7	18.0	5.3	6.8	38.2	38.3	34.0	36.0
Average	20.1	21.49	8.4	9.01	41.2	40.2	36.2	39.4

before treatment. The number of white cells has also increased from an average of 9,359 to 11,166. Hemoglobin, differential counts of the white cells and determinations of urea nitrogen, sugar, uric acid, cholesterol, whole blood chloride, serum calcium and serum phosphate all show average results similar to those obtained during addiction. Dry matter of the plasma and of the whole blood has increased slightly, with a slight fall

in the dry matter of the cells. The average  $p_H$  of the blood has risen from 7.36 to 7.41 following treatment, the carbon dioxide capacity of the plasma having fallen from 57.7 to 52 per cent by volume. The average per cent by volume of the red blood cells has increased slightly from 36.2 to 39.4, while the lactic acid of the blood also shows a slight increase following treatment from an average of 25 to 31 mg per hundred cubic centimeters of blood.

Sedimentation tests in twelve cases before and after treatment showed parallel curves indicating no change. Studies of the viscosity of the blood in five cases showed no difference before and after treatment.

*Metabolism*—The basal metabolic rates of ten addicts obtained during the administration of morphine and again after treatment remained strikingly constant. The average range before treatment was between  $-9$  and  $+9$  and following treatment between  $-14$  and  $+9$ . Individual determinations showed the lowest and highest rates before treatment to be  $-26$  and  $+28$  and following treatment  $-28$  and  $+26$ .

*Changes in Weight*—The loss of weight during treatment in some cases was striking. Twenty patients whose weights were taken just before and after treatment showed an average loss of 7 pounds (3.2 Kg). The greatest loss was 18 pounds (8.2 Kg), while one patient actually gained 3 pounds (1.4 Kg). The other eighteen cases showed losses of weight of from 2 to 12 pounds (0.9 to 5.4 Kg), respectively.

*Temperature*—Temperatures taken in a series of 100 addicts during treatment and for a period of three days following the cessation of the administration of scopolamine showed a slight rise for forty-eight hours in seventy-eight of the cases. The highest temperature recorded was 100.8 F, the average maximum temperature in the seventy-eight cases being 99.4. These patients were all free from abscesses and intercurrent infections. This slight rise in temperature rarely continued for more than forty-eight hours, although one addict had an average temperature of 99.2 for a period of five days, which rose at times to as high as 100.

*The Kidneys*—The urines of 100 addicts showed a definite rise in the average specific gravity of from 1.018 to 1.026, with a distinctly lower twenty-four hour output following treatment. In two cases, a trace of sugar was found with Benedict's test following treatment. Thirty-two cases showed the presence of from a trace to a light cloud of albumin, ten cases showing a few granular and hyaline casts. Spermatozoa were frequently found in the urine following treatment.

Phenolsulphonphthalein tests in eight cases studied before and after treatment showed an average two hour elimination of 64 per cent of the dye before treatment and of 48 per cent after treatment. Five of these eight cases showed albumin in the urine following treatment, one

case showing a light cloud. The latter patient eliminated 49 per cent of the dye before treatment and only 16 per cent following treatment during the two hour periods. The other seven cases showed slight decreases in the amounts excreted after treatment compared to the results obtained during the administration of morphine.

*The Liver*—The phenoltetrachlorophthalein test carried out in four cases showed no delay in the disappearance of the dye in two hours either before or after treatment. Van den Bergh's tests remained negative in four cases both before and after treatment. An average icterus index of 6.1 was obtained following treatment as compared to an average of 5.5 obtained before treatment.

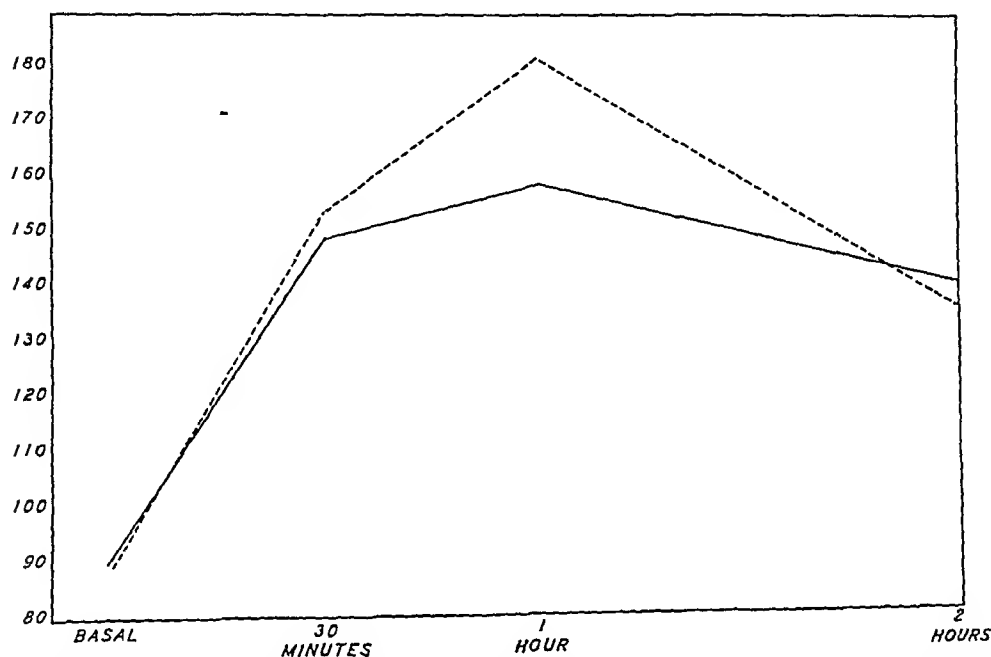


Chart 3—Average blood sugar response to the injection of 1 cc of epinephrine hydrochloride (1:1,000) in a group of human addicts receiving morphine, and after treatment with scopolamine.

*Blood Sugar Response to Epinephrine*—Chart 3 shows graphically the blood sugar response in a series of five addicts who were given 1 cc of 1:1,000 epinephrine hydrochloride both before and after treatment. The curves show that the blood sugar content rises slightly higher following treatment as compared to the rise while morphine is being administered. Determinations of blood pressure were also made, but the results were so variable as to make any comparison doubtful in value.

#### COMMENT AND LITERATURE

The interpretation of our results in the light of the behavior and appearance of the addicts following treatment is extremely difficult.

The effect of the diastolic purgation and the scopolamine itself must be considered in the production of the changes observed, but in general

our observations following treatment are more or less similar to those obtained during a series of studies made following a forty-eight hour period of abrupt withdrawal without the substitution of any other drug<sup>3</sup>

Lambert and Tilney<sup>4</sup> studied the blood of a series of opium addicts before and during treatment with narcosan. They did not find any changes in the uric acid and creatinine of the blood either before or during treatment. Wide fluctuations of the blood sugar, which we interpret as being standard, are reported one hour after breakfast was taken. Our blood sugar values remained constant in specimens taken before and after treatment while the addict was fasting. Lambert and Tilney<sup>4</sup> also found considerable fluctuation of the carbon dioxide chemically bound in the plasma and detected an increase in acidosis for the first three days of treatment. In the majority of our cases, the average  $p_H$  of the blood shows a tendency for a slight increase in the alkalinity following treatment. Our blood cell determinations are similar to those obtained by Lambert and Tilney except that we encountered certain slight degrees of leukocytosis before treatment was begun. Our urinary observations are also identical with those of Lambert and Tilney.<sup>4</sup>

In a comparative study of the efficiency of the narcosan treatment with the routine treatment employed in the Colorado Psychopathic Hospital, Johnson<sup>5</sup> was unable to detect any significant changes in the blood. He found but one abnormal blood sugar value, while his figures for blood urea nitrogen were well within normal limits. Johnson found a leukocytosis in most cases during narcosan treatment, the actual figures obtained ranging between 5,400 and 19,300 cells.

Immediately following treatment, the appearance and behavior of the addicts are misleading. It has been our frequent experience to have two addicts in the ward whose needs were supplied with the same amount of morphine and who were given identical treatment at the same time. At the end of the fourth day, one addict will be up and about the ward with the declaration that he feels fine and will eat well and boastfully proclaim that he is through with the drug. The other addict will remain in bed, refuse food, appear miserable and complain bitterly of extreme weakness and nervousness. We believe that frequently neither of these two types is expressing or acting his real self. The addict who proclaims his well-being may or may not show the few posi-

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3 Light, Arthur B., and Torrance, Edward G. Opium Addiction. VI. The Effects of Abrupt Withdrawal Followed by Readministration of Morphine in Human Addicts with Special Reference to the Composition of the Blood, the Circulation and the Metabolism, *Arch Int Med* **44** 1 (July) 1929.

4 Lambert, Alexander, and Tilney, Frederick. Treatment of Narcotic Addiction by Narcosan, *M J & Rec* **124** 764 (Dec 15) 1926.

5 Johnson, George S. The Use of Narcosan in the Treatment of Drug Addiction, *Colorado Med* **24** 347 (Nov) 1927.

tive changes we have previously noted. We are convinced that a good deal of this behavior is feigned, and that the addict is trying to gain his discharge in order that he may return to his friends who will again supply him with drugs.

The other addict who complains of being so miserable and weak and nervous may or may not show any of the positive symptoms previously mentioned. This behavior is frequently found in addicts who are penniless and who do not know where to turn for drugs when discharged from the ward.

It is during this period of the addict's stay in the ward that our method of treatment is characterized as being the best or the worst that the addict has ever undergone.

Few of our addicts have not had treatments before. Many of them have tried every method employed for the treatment of narcotic addiction. Their comments as to the efficacy of these various forms of treatment are totally unreliable. It is our opinion, however, from the number of addicts who have come to us from other institutions and the fact that 50 per cent come back to us for another treatment, that present methods, including our own, leave much to be desired.

#### CONCLUSIONS

Studies of a series of opium addicts before and after treatment with scopolamine revealed the following positive changes: loss of weight, slight rise in temperature, appearance of albuminuria, slight leukocytosis, slight concentration of the blood, a rise in the  $p_H$  of the blood, a rise in the lactic acid of the blood, a fall in the carbon dioxide capacity and a fall in the total number of points scored with Schneider's test of physical fitness.

No significant changes were found in a comparison of the pulse, respiration rates and blood pressure while the addict was reclining, heart measurements, electrocardiographic studies, staircase climbing tests, effect of atropine sulphate on the P-R interval, vital capacities, blood urea nitrogen, blood sugar, blood uric acid, blood cholesterol, whole blood chloride, serum calcium and phosphate, blood viscosity, sedimentation tests, basal metabolism, phenolsulphonphthalein tests, phenol-tetrachlorophthalein test of liver function, icterus index, van den Bergh's tests, and response of the blood sugar to epinephrine.

The few positive observations do not coincide with the general appearance and behavior of the addict. He may present some or all of the foregoing positive symptoms and yet appear and behave as though he were normal. On the other hand, he may give the appearance of one who is quite ill and yet not show any of the foregoing positive symptoms.



# BLUEBERRY LEAF EXTRACT OVERDOSAGE

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In a recent paper<sup>1</sup> I corroborated the work of Allen<sup>2</sup> on blueberry leaf extract now called "myitomet," and extended it further by investigating its effect on thyroid hyperglycemia and glycosuria. Because of the possible demand for blueberry leaf extract in treating patients with mild diabetes, it seemed imperative at this time to study the effect of overdosage with blueberry leaf extract, particularly since von Noorden<sup>3</sup> published data purporting to show that this drug causes focal necrosis in the liver following intravenous injection. It seemed to me that this method of biologic assay is unwarranted, since the preparation of the drug available at the present time is too crude for parenteral, least of all intravenous, injection. Because of these considerations, it seemed important to determine whether the oral administration of the drug in dosages even greater than those prescribed for man exerted any detectable deleterious effect.

## METHODS

Four dogs were put on a daily standard diet of 250 Gm of beef heart, 100 Gm of bread and 250 cc of milk. This diet, sufficient for their caloric needs, was not changed during the course of the experiment. The total output of urine was recorded and samples were taken for daily analysis. Toluene was used as a preservative to minimize bacterial decomposition. At the time the samples of urine were taken, from 5 to 6 cc of blood was withdrawn from the saphenous vein and put in tubes containing powdered potassium oxalate as an anticoagulant.

To test qualitatively for urinary sugar, Fehling's or Benedict's reagents were used. If the tests were negative, the samples were discarded, if positive, the amount of blood and urinary sugar was determined by the method of Folin-Wu, two determinations being made on each sample.

The Folin-Wu method was used to determine the amount of blood sugar. Two blood sugar determinations were made daily, the average being recorded as the blood sugar level for that day.

Control experiments were made on the animals three or more days before preparing them for initial experiments.

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<sup>1</sup> From the Hull Physiological Laboratory, University of Chicago

<sup>2</sup> Aided by a grant from the Frank Billings Medical Research Club, Chicago

1 Shpiner, L B. Am J Physiol **84** 396, 1928

2 Allen F M. Blueberry Leaf Extract. Physiologic and Clinical Properties in Relation to Carbohydrate Metabolism, J A M A **89** 1577 (Nov 5) 1927

3 Von Noorden, C. Die Zuckerkrankheit und ihre Behandlung, Berlin, A Hirschwald, 1927. Blueberry Leaf Extract. Preliminary Report of Council on Pharmacy and Chemistry. J A M A **89** 1607 (Nov 5) 1927

The effect of overdosage with blueberry leaf extract was studied on two normal and two partially pancreatectomized dogs. After a control period of three or more days, the dogs were operated on. Pieces of liver and pancreas were removed for microscopic examination. In performing a partial pancreatectomy, nineteen twentieths of the pancreas was removed, the remnant being connected to the duodenum through the duct of Santorini. At the conclusion of the experiment, a biopsy was again performed. The removed hepatic and pancreatic tissue was fixed, stained and compared with the sections of the liver and pancreas taken from the animal when it was in a normal state.

In studying the effects of blueberry leaf extract,<sup>4</sup> from six to twelve tablets (5 grams [0.324 Gm.] per tablet) were given at least one hour before feeding time. This dosage represents from two to four times the dosage of blueberry leaf extract necessary for its therapeutic effect in man.

Sections of the pancreas were fixed with Bensley's<sup>5</sup> A O B and stained for study of islet tissue, and also with hematoxylin and eosin. Sections of the liver were stained with Best's<sup>6</sup> carmine method for glycogen.

Phenolsulphonphthalein was used in studying renal function. The drug was administered intravenously, and collections of urine for a study of the rate of elimination of the dye were limited to one hour.

(a) Normal dogs were fed a control diet for twelve days. The low blood sugar content was 80 mg. per hundred cubic centimeters, the high content was 90 mg. The urine did not contain sugar. The average volume of urine was 250 cc. The average amount of phenolsulphonphthalein excreted in the first hour was 76.6 per cent.

(b and c) A piece of liver and pancreas was removed for microscopic examination. In the postoperative period (seven days) the dogs were maintained on a high fluid diet plus six tablets of blueberry leaf extract. The low blood sugar content was 84 mg. per hundred cubic centimeters, the high content was 91 mg. The urine did not contain sugar. The average volume of urine was 202 cc. The average excretion of phenolsulphonphthalein in the first hour was 80 per cent.

(d) A control diet plus six tablets of blueberry leaf extract were given for eight days. The low blood sugar content was 85 mg. per hundred cubic centimeters, the high content was 92 mg. The urine did not contain sugar. The average volume of urine was 316 cc. The average amount of phenolsulphonphthalein excreted in the first hour was 76.7 per cent.

(e) A control diet plus twelve tablets of blueberry leaf extract were given for fifteen days. The low blood sugar content was 81 mg. per

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4 The blueberry leaf extract used in these experiments was furnished by E. R. Squibb & Sons, New Brunswick, N. J.

5 Bensley, R. R. Harvey Lectures, 1914-1915, p. 250. The formula for Bensley's A O B fixing fluid is: glacial acetic acid, 1 drop; 2 parts of 2 per cent aqueous solution of osmic acid, and 8 parts of 3 per cent potassium bichromate.

6 Best. Pathological Technique, ed. 8, Philadelphia, Mallory & Wright, 1924, p. 199.

hundred cubic centimeters, the high content was 89 mg. The urine did not contain sugar. The average volume of urine was 280 cc. The average secretion of phenolsulphonphthalein in the first hour was 78.7 per cent.

(f) A control diet plus six tablets of blueberry leaf extract were given for eight days. The low blood sugar content was 82 mg. per hundred cubic centimeters, the high content was 85 mg. The urine did not contain sugar. The average volume of urine was 280 cc. The average excretion of phenolsulphonphthalein in the first hour was 76.6 per cent.

(g) A control diet and blueberry leaf extract were given for eight days. At the end of this time, the low blood sugar content was 84 mg. per hundred cubic centimeters, the high content was 90 mg. The urine did not contain sugar. The average volume of urine was 316 cc. The average amount of phenolsulphonphthalein excreted in the first hour was 78.3 per cent.

(h) A control diet plus twelve tablets of blueberry leaf extract were given for forty-three days. The low blood sugar content was 83 mg. per hundred cubic centimeters, the high content was 98 mg. The urine did not contain sugar. The average volume of urine was 316 cc. The average excretion of phenolsulphonphthalein in the first hour was 77 per cent.

At the end of the experiment, a piece of liver and one of pancreas were fixed, stained and examined microscopically.

As can be seen from the results given, blueberry leaf extract in from two to four times the therapeutic dose has no effect on normal dogs. The blood sugar remains normal and there is a slight polyuria, but the rate of the excretion of phenolsulphonphthalein remains within normal limits. During the experimental period, the temperature, pulse, respiration and body weight do not vary from the normal. Microscopic examination of the pancreas fixed and stained with the A O B method and hematoxylin and eosin shows no increase in the islet or acinar tissue. Sections of the pancreas resemble normal pancreas taken during the control period.

Best's carmine method for glycogen reveals neither an increase nor a decrease in glycogen content of the liver cells.

The results obtained on the partially pancreatectomized dogs (nineteen-twentieths) were as follows:

(a) A dog was fed a control diet for six days. The low blood sugar content was 80 mg. per hundred cubic centimeters, the high content was 86 mg. The urine did not contain sugar. The average volume of urine was 317 cc. The average excretion of phenolsulphonphthalein in the first hour was 78.3 per cent.

(*b* and *c*) A subtotal pancreatectomy was performed (nineteen-twentieths of the gland was removed) In the postoperative control period (*c*) the animal was given a fluid diet plus six tablets of blueberry leaf extract for five days The low blood sugar content was 85 mg per hundred cubic centimeters, the high content was 130 mg The urine did not contain sugar The average volume of urine was 216 cc The average amount of phenolsulphonphthalein excreted was 80 per cent

(*d*) An animal was fed a control diet plus six tablets of blueberry leaf extract for ten days The low blood sugar content was 98 mg per hundred cubic centimeters, the high content was 130 mg The urine did not contain sugar The average volume of urine was 351 cc The average amount of phenolsulphonphthalein excreted in the first hour was 80 per cent

(*e*) An animal was fed a control diet plus twelve tablets of blueberry leaf extract for seventeen days The low blood sugar content was 91 mg per hundred cubic centimeters, the high content was 97 mg The urine did not contain sugar The average volume of urine was 335 cc The average excretion of phenolsulphonphthalein in the first hour was 79 per cent

(*f*) A control diet plus six tablets of blueberry leaf extract were given the animals for seven days The low blood sugar content was 82 mg per hundred cubic centimeters with a high content of 89 mg The urine did not contain sugar The average volume of urine was 426 cc The average excretion of phenolsulphonphthalein in the first hour was 77.5 per cent

(*g*) A control diet of twelve tablets of blueberry leaf extract was given for eighteen days The low blood sugar content was 88 mg per hundred cubic centimeters, the high content was 102 mg The urine did not contain sugar The average volume of urine was 439 cc The average excretion of phenolsulphonphthalein in the first hour was 77 per cent

(*h*) A control diet without blueberry leaf extract was given to the dogs for seven days The low blood sugar content was 90 mg per hundred cubic centimeters, with a high content of 98 mg The urine did not contain sugar The average volume of urine was 417 cc The average amount of phenolsulphonphthalein excreted in the first hour was 77.5 per cent

(*i*) A control diet plus twelve tablets of blueberry leaf extract were given for fourteen days The low blood sugar content was 86 mg per hundred cubic centimeters, the high content was 98 mg The urine did not contain sugar The average volume of urine was 408 cc The average excretion of phenolsulphonphthalein in the first hour was 78 per cent

At the end of the experiment a piece of pancreas and a piece of liver were removed, fixed, stained and examined microscopically

Removal of nineteen-twentieths of the pancreas leads to diabetes, in the dogs kept on doses of blueberry leaf extract, however, diabetes did not develop. The experiment corroborated results obtained by Allen on similar dogs. In only one of the dogs did hyperglycemia develop after removal of the blueberry leaf extract from the diet. But on subsequent feeding of blueberry leaf extract followed by its removal from the diet, a hyperglycemia and glycosuria did not again develop. During the experimental period, the temperature, pulse, respiration and body weight did not vary from those of the normal period.

Here, as well as in normal dogs, no derangement of kidney function was noted. The hyperglycemia and glycosuria were controlled by the feeding of blueberry leaf extract, and the excretion of phenolsulphonphthalein dye remained within normal limits.

Microscopic sections of pancreas, as examined by Bensley's A O B method and hematoxylin and eosin, showed regeneration of acinar, but not of islet tissue.

Sections of the liver examined by Best's carmine stain showed about the same amount of glycogen as in the sections of normal liver. This indicates that there was no depletion in the amount of glycogen in the liver following the period of partial pancreatectomy plus the feeding of blueberry leaf extract. Furthermore, there was no indication of focal necrosis.

#### COMMENT

The results in my experiments indicate that overdosage with blueberry leaf extract (myrtomel), both in normal and in partially pancreatectomized dogs, is without detectable effect. Assuming that the average weight of a dog is one-fifth that of man, I have fed dogs, on the basis of body weight, twenty times the therapeutic dose over a period representing 49 per cent of the life span of man without any noticeable untoward systemic effects.

#### CONCLUSIONS

On the basis of my experiments I conclude that

Blueberry leaf extract is nontoxic to normal and partially pancreatectomized dogs when administered orally in what may be considered excessive doses.

Its clinical trial in diabetes, therefore, is not fraught with any undesirable effects or possibilities.

# THE RETICULOCYTE COUNT IN NORMAL AND IN ABNORMAL CONDITIONS \*

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CINCINNATI

Since the advent of vital staining, interest in the reticulocyte count as one index of regeneration of the blood has been much heightened

Among the earlier investigators to study reticulation was Ehrlich,<sup>1</sup> who by means of a dried blood film stained with a saturated solution of methylene blue (methylthionine chloride, U S P ), described nets in the red corpuscles in normal blood and in anemia Twelve years later Askanazy<sup>2</sup> noted a reticulated substance in the erythrocytes of a rapidly progressive anemia In 1901, Levaditi<sup>3</sup> began the use of a brilliant cresyl blue as a vital stain, but did not mention reticulation From 1907 to 1913 much work was done on reticulation A brief summary of these studies will be found in Cunningham's article<sup>4</sup> In his own work Cunningham<sup>4</sup> found that permanent preparations could be made by combining a vital stain with Wright's stain He thought that the ease and simplicity of this method would bring the study of reticulated erythrocytes within the scope of routine blood examinations In this method a small drop of 0.3 or 0.5 per cent solution of brilliant cresyl blue is placed on a clean slide or cover glass, smeared around over an area of 1.5 cm. and allowed to dry A drop of blood on a cover-slip is then dropped face down on the area of dried stain After drying, the film is stained with Wright's stain This method is similar to that advocated by Hawes<sup>5</sup> in 1909

Many authors use this method also for the counting of the reticulocytes One thousand red cells are counted in fields of about fifty, the reticulated cells seen during the counting process being enumerated This method is open to the criticisms that the dye or cells or both may not be evenly spread, that some of the reticulated cells may wander to the edges and that the dye might not penetrate a thick specimen

For these reasons and for the purpose of securing the greatest possible accuracy in reticulate counts, we have adopted another method to be described presently

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1 Ehrlich, P. *Berl klin Wchnschr* **3** 43, 1881

2 Askanazy, S. *Ztschr f klin Med* **23** 80, 1893

3 Levaditi, C. *J de physiol et de path gen* **3** 425, 1901

4 Cunningham, T. D. *Method for Permanent Staining of Reticulated Red Cells*, *Arch Int Med* **26** 405 (Oct) 1920

5 Hawes, J. B., Jr. *Boston M & S J* **161** 493, 1909

Krumbhaar<sup>6</sup> drew the blood to be counted into a leukocyte counting pipet, using a dilute solution of brilliant cresyl blue as the diluent. After thorough shaking, a wet cover slip preparation is made from the content of the pipet, mixed with petrolatum and then counted in the usual manner, counting 1,000 cells.

Seyfarth<sup>7</sup> used a fresh preparation with a square cover glass and an ocular graduated for counting. He emphasized the fact that stained slides are not good for the counting of reticulocytes, as the methyl alcohol fixation causes some of the granules to disappear. He also thought that the centrifugation methods of Abram and Biule are not applicable for reticulocyte counting. After centrifugation the granule-containing cells are not evenly distributed throughout the entire mass.

McCord,<sup>8</sup> desiring a quick and approximately quantitative method to be used chiefly among lead workers, used the following. He made a thick smear of blood and, without fixing, stained with a dilute solution of a modified Manson's methylene blue. With this stain, only the shadowy outlines of the normal erythrocytes are seen, while the reticulocytes and stippled cells show blue reticulation or granules within this outline. He then counted the number of such cells in ten oil immersion fields and took the average number per field. The objections to this method are that it is not accurately quantitative and that the stain is relatively unstable. We have found that a solution of polychrome methylene blue will give the same results, and that it is much more stable.

#### METHOD

The method we have worked out has been described in a previous paper.<sup>9</sup> Because of its simplicity, and because of recent modifications, it is described in detail here.

A specific pipet for the making of a blood dilution of 1:20, instead of the usual white cell pipet (dilution 1:10), is used. A microscopic objective, giving a magnification higher than the ordinary 4 mm lens, is of advantage. We have used a no. 7 Leitz or a DD Zeiss. The oil immersion lens cannot be used.

The solutions needed are

1. A 1 per cent aqueous solution of brilliant cresyl blue. We have used the Gruebler, natural aniline and Coleman-Bell dyes. The Coleman-Bell dye has given the best results.
2. A diluent solution containing 0.6 Gm. of sodium chloride and 0.2 Gm. of potassium oxalate to 100 cc. of distilled water.

6 Krumbhaar, E. B. *J. Lab. & Clin. Med.* 8:11, 1922-1923.

7 Seyfarth, C. *Folia haemat.* 34:7, 1927.

8 McCord, C. P. The Basophilic Aggregation Test in Lead Poisoning. *J. A. M. A.* 82:1759 (May 31) 1924, *Bull. U. S. Bureau Labor Statistics*, April, 1928, no. 460.

9 Friedlander, A. and Wiedemer, C. Basophilic Aggregation in New-Born, *Am. J. Dis. Child.* 30:804 (Dec.) 1925.

These are the stock solutions. They can be kept indefinitely in a cool place. As needed, another dilute solution is made up as follows:

Two cubic centimeters of the brilliant cresyl blue solution (solution 1) is added to 8 cc of the diluent solution (solution 2), which makes a 0.2 per cent solution of brilliant cresyl blue. This solution (solution 3) must be made up fresh about once a week. It is necessary to vary the dilution from time to time, depending on the dye used.

The blood is drawn up to the 0.5 mark of the pipet with a dilution of 1:20, then it is diluted to the 21 mark with the 0.2 per cent brilliant cresyl blue solution (solution 3). The pipet is shaken thoroughly, allowed to stand for ten minutes or more and then shaken well again. The blood is then ready for counting. The ordinary counting chamber is used, and the squares are counted as they are in the ordinary white cell count. In calculating the result it must be remembered that the dilution is twice that of the ordinary white cell count. The blood, diluted in this way, may stand twenty-four hours without injury to the cells, but after this period the count is not accurate. To count the reticulocytes, it is necessary to have a good light, preferably artificial, and an especially high magnification dry lens as before mentioned. With this dilution of stain, the white blood cells stain dark blue. The red cells have a pale yellow cast, but show up blue. The reticulocytes are easily recognized by the blue reticulum or granules in their cytoplasm. The various forms of reticulocytes, as enumerated by Seyfarth,<sup>7</sup> are brought out distinctly. These vary from the earliest forms, with dense reticulum in the center of the cells so that they resemble normoblasts, to the more mature forms showing only a few scattered basophilic granules.

When normoblasts or megaloblasts are present, there is a distinct difference in staining reaction between the nuclear and reticular material. The nuclear material stains purple, the reticular substance stains blue.

This method overcomes the chief objections to the Cunningham method,<sup>4</sup> which is the method in general use. In the Cunningham method the stain does not come in contact with all cells of the blood droplet, and the reticulocytes are not evenly distributed over the slide. It is much simpler than counting 1,000 red cells in a stained preparation. As a matter of fact, by this method a reticulocyte count can be done as easily, and almost as quickly, as a white cell count after some experience has been had with the method.

#### EXPERIMENTAL STUDIES

The figures as to the reticulocyte count in normal persons, as given in the literature, show great variations. It is even stated that the normal reticulocyte count runs to 1 or 1.5 per cent of the red cell count. On a basis of 5,000,000 red cells, this would mean an average of from 50,000 to 75,000 reticulocytes per cubic millimeter for the normal person. We are convinced that these figures are much too high. As a basis for our studies of the reticulocyte count in pathologic conditions, and as a test of our method, we made complete blood counts, including reticulocyte counts, on ninety-three persons, all in good health as far as we could ascertain. In addition to the complete count, the reticulocyte count was done, in each instance, by three methods, *i. e.*, Cunningham's, McCord's and our own.



As our figures for the reticulocyte count, however, were lower than those usually given in the literature, the criticism of our method was made that the diluting stain hemolyzed the reticulocytes. This would give us lower counts. *A priori* we felt that this criticism was probably not justified because, as has been shown by Buckman and MacNaugher,<sup>10</sup> reticulocytes, except in pernicious anemia, are less fragile than mature erythrocytes. To meet this criticism, however, we made parallel counts on seventy-two of the normal persons studied. In one red cell count we used the Hayem's solution as ordinarily employed. In the other, we used, as the blood diluting fluid, the 0.2 per cent brilliant cresyl blue solution, as used for our reticulocyte counts. These red cell counts, as shown by our studies, vary only between experimental limits.

The reticulocyte count on normal persons is also compared in the accompanying tables, as done by the Cunningham, McCord and our method. One series of counts was made during the winter months, a second was made during the spring months. In forty-six normal persons studied during the winter months (from November 17 to March 10), the counts ran as follows: Cunningham, from 0 to 0.7 per cent, average 0.22 per cent, McCord, from 0 to 1.8 per cent, average 0.4 per cent, Friedlander and Wiedemer, from 0 to 0.1 per cent, average 0.03 per cent. In forty-seven normal persons studied during the spring months (from March 10 to May 30), the figures were as follows: Cunningham, from 0 to 1 per cent, average 0.3 per cent, McCord, from 0.2 to 1.7 per cent, average 0.78 per cent, Friedlander and Wiedemer, from 0.03 to 0.4 per cent, average 0.18 per cent.

It will be noted that during the winter months, the counts on normal persons were seven times as high by the Cunningham method as by our method, during the spring months, they were twice as high. In each instance figures for the McCord method were twice as high as those for the Cunningham method.

We are convinced, as shown by our accurate quantitative counts, that the figures as ordinarily reported for the reticulocyte count in normal persons are much too high. We believe that the reticulocyte count in normal persons runs from about 0.03 to 0.2 per cent, that is, from 1,500 to 10,000 reticulocytes per cubic millimeter, depending on the time of the year. We are also inclined to the belief that by our method the reticulocyte counts on normal persons run much more consistently than by the Cunningham method, which gives a much greater variation than we obtain.

The foregoing counts were done on healthy adults of both sexes between the ages of 20 and 50. Most of them were physicians, nurses and medical students. The counts were begun in the winter and all

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10 Buckman T E, and MacNaugher, E. J. M. Research 44 61, 1923

ran low—from 1,000 to 2,000 reticulocytes per cubic millimeter. As the work continued into the spring months, the counts began to run higher, up to 20,000. Thinking that there might be a definite seasonal variation, we made rechecks of counts on persons on whom the counts had been made during the winter months. The results in sixteen of the persons studied are shown in table 1.

In each instance, comparative counts on the same person made during the winter and spring months are shown on the same line of table

TABLE 1—*Reticulocyte Counts on Normal Adults During Winter and Spring Months*

Patient	Date	Red Count	Reticulocyte Count	Date	Red Count	Reticulocyte Count
5	Jan 6	4,810,000	800	April 5	6,660,000	16,000
31	Jan 13	4,860,000	400	April 11	5,500,000	16,800
70	Jan 6	6,480,000	0	April 11	6,050,000	3,600
68	Jan 7	6,100,000	0	April 21	5,460,000	21,000
29	Feb 16	4,940,000	600	April 11		8,400
30	Feb 16	5,410,000	800	April 4		10,000
32	March 7	4,020,000	1,000	April 18	4,940,000	10,000
34	March 7	4,680,000	1,600	April 1		21,000
36	March 8	5,820,000	4,000	April 9		5,600
38	March 8	4,990,000	3,000	April 12		21,600
39	March 8	4,120,000	2,000	April 12		11,200
45	March 10	5,490,000	2,000	April 29	5,620,000	4,400
47	March 10	5,240,000	4,000	April 9		24,800
48	March 11	4,160,000	2,800	April 11		12,000
51	March 11	4,970,000	2,400	April 12		6,000
52	March 11	3,790,000	2,000	April 12		6,000

TABLE 2—*Repeated Reticulocyte Counts in a Normal Adult*

Date	Hemoglobin, Per Cent	White Count	Red Count	Reticulocyte Count
3/20/27	70	5,000	4,460,000	3,600
3/21/27				4,800
3/22/27				6,000
3/25/27				6,600
3/28/27				5,600
4/13/27				7,000
4/20/27				14,000
5/ 3/27				20,000
5/17/27				4,000
5/25/27				4,800
6/25/27	80	6,400	4,870,000	6,000
7/25/27				8,800
10/14/27				5,000
3/ 5/28			4,680,000	6,000

1. The counts were invariably higher during the spring months, although even at this time the highest figure obtained was 0.4 per cent (number 47). Our figures, as found during the spring and summer months, check closely with those of Seyfarth.<sup>7</sup> The probable explanation for the increased count during the spring months is that of the general stimulation of the body produced by the increase in ultraviolet rays from the sun at that time. In this connection, it may be noted that check counts done at the Taft heliotherapy ward at the Cincinnati General Hospital, where both natural and artificial rays are used showed an increase in the reticulocyte count after heliotherapy. In table 2

are shown the reticulocyte counts on a healthy adult, as found at intervals during a year's time. Tables 3 and 4 show the change in the reticulocyte count in healthy adults from the winter to the spring months.

In connection with these studies and with particular reference to the reticulocyte count in benzene poisoning (which is to be the subject

TABLE 3—*Repeated Reticulocyte Counts in the Same Person (a Normal Subject), Showing Rise of Reticulocyte Count During the Spring Months*

Date	Hemoglobin, Per Cent	White Count	Red Count	Reticulocyte Count
1/ 6/26	80	9,200	4,810,000	800
11/19/26	90	10,000	6,060,000	6,400
1/28/27				400
3/20/27				16,000
3/21/27				16,800
4/ 5/27				16,000
5/18/27	80	8,400	5,320,000	14,200

TABLE 4—*Repeated Reticulocyte Counts in H W, a Normal Adult, Showing Rise of the Reticulocyte Count During the Spring Months*

Date	Hemoglobin, Per Cent	White Count	Red Count	Reticulocyte Count
1/13/27	75		4,860,000	400
2/16/27	70	7,000	4,640,000	1,200
4/11/27	80			16,800
5/26/27	80	8,000	5,500,000	16,400
11/14/27	80	9,000	4,710,000	9,200

TABLE 5—*Reticulocyte Counts on Full-Grown Rabbits\**

Date	Rabbit Number	White Count	Red Count	Reticulocyte Count
June 14	1	16,400	5,480,000	72,000
June 18	2	7,600	5,440,000	40,000
July 7	3	10,200	6,080,000	23,200
July 16	4	16,600	5,280,000	80,000
July 23	5	9,200	5,440,000	34,000
July 24	6	16,400	6,240,000	42,000
Dec 24	7	7,800	5,540,000	14,000
Dec 17	8	9,800	5,120,000	29,400
Dec 12	9	10,600	5,460,000	28,000
March 14	10	8,200	5,840,000	36,000
March 11	11	9,400	6,280,000	18,000
April 2	12	8,000	5,240,000	41,000

\* The reticulocyte counts in rabbits vary within wide limits and are higher than those in normal human beings.

of another paper), we made reticulocyte counts on a number of laboratory animals. In earlier studies on benzene poisoning, the white blood counts on rabbits were used as indexes. We have found that the reticulocyte counts in full grown rabbits are much higher than those in human beings. Furthermore, there is great individual variation. These facts are set forth in table 5.

In guinea-pigs the reticulocyte counts in our studies approximated the figures as found for human beings (table 6).

The counts in monkeys and in dogs were approximately the same as in human beings

In cats, we found the reticulocyte count to be somewhat lower than it is in human beings (table 7)

TABLE 6—*Reticulocyte Counts in Normal Full-Grown Guinea-Pigs*

Date	Guinea-Pig Number	White Count	Red Count	Reticulocyte Count
Jan 23	1	7,400	5,480,000	16,000
Jan 23	2	8,600	6,480,000	7,800
Jan 23	3	8,200	5,600,000	8,000
June 28	4	9,600	5,640,000	12,800
July 11	5	12,800	6,480,000	6,400
July 11	6	8,900	4,960,000	8,000
July 11	7	9,800	5,480,000	12,400
July 11	8	14,200	5,780,000	4,800
June 16	9	8,000	5,360,000	5,800
June 16	10	9,200	5,120,000	12,600
June 13	11	9,800	5,960,000	8,000
Sept 1	12	8,600	6,160,000	9,800

\* The reticulocyte count in guinea pigs is similar to that of human beings

TABLE 7—*Reticulocyte Counts on Full-Grown Cats\**

Date	Cat Number	White Count	Red Count	Reticulocyte Count
June 13	1	12,800	5,400,000	800
June 14	2	9,800	5,640,000	200
July 11	3	24,800	6,120,000	400
July 12	4	18,800	5,520,000	1,400
July 14	5	20,400	5,840,000	200
Sept 8	6	34,000	5,720,000	2,400
Sept 1	7	18,000	5,640,000	200
Sept 1	8	22,000	5,880,000	200
Sept 4	9	10,800	6,120,000	800
June 14	10	15,400	6,200,000	1,400

\* Cats show a somewhat lower reticulocyte count than human beings

Our studies would thus have given the following normal averages

Man	0.03 to 0.2 per cent
Rabbit	0.25 to 1.5 per cent
Guinea-pigs	0.08 to 0.29 per cent
Cats	0.003 to 0.04 per cent

The foregoing figures may be compared with those of Kumbhaar,<sup>6</sup> who, using a different method of counting, gave the following averages

Man	0.1 to 0.8 per cent
Rabbit	0.6 to 2.8 per cent
Guinea-pigs	1.0 to 4.0 per cent
Cat	0.0 to 0.4 per cent

In an earlier paper<sup>9</sup> we showed the physiologic increase in the reticulocyte count in the new-born infant. In table 8, taken from this paper, reticulocyte counts in the new-born infant are shown. These figures check fairly well with the counts of other observers.

TABLE 8.—Quantitative Estimation of Basophilic Cells to the Cubic Centimeter of Blood in the New-Born Infant  
*Blood Pipet and Counting Chamber Polychrome Methylene Blue*

Sex	Color	Age	Date and Count											
			2/ 6/25—18,000	2/ 7/25—16,400	2/ 9/25—14,000	2/10/25—11,200	2/12/25—6,000	2/13—4,300	2/14—1,200	2/16—230	2/17—20			
♀	W	1 hour	2/ 6/25—18,000	2/ 7/25—16,400	2/ 9/25—14,000	2/10/25—11,200	2/12/25—6,000	2/13—4,300	2/14—1,200	2/16—230	2/17—20			
♂	O	12 hours	2/ 9/25—16,000	2/10 —14,000	2/11 — 9,400	2/12 — 8,800	2/13 —4,200	2/14—2,000	2/16— 270	2/17—130	2/18—25			
♀	W	12 hours	2/16/25—16,400	2/17 —14,000	2/18 —11,200	2/19 — 7,000	2/20 —4,800	2/21—2,000	2/23— 750	2/24— 10				
♂	W	18 hours	2/17/25—17,000	2/18 —15,000	2/19 —12,800	2/20 — 9,400	2/21 —6,100	2/23—2,000	2/24— 150	2/25— 10				
♂	W	6 hours	3/ 9/25—17,000	3/11 —14,400	3/13 —11,000	3/16 — 4,200	3/18 —1,000	3/20 20 } Twins						
♂	W	6 hours	3/ 9/25—15,800	3/11 —13,800	3/13 —10,800	3/16 — 3,200	3/18 — 450	3/20 10 }						
♂	O	12 hours	3/16/25—14,800	3/18 —10,000	3/20 — 4,000	3/23 — 250	3/25 — 10							
♂	W	7 months	3/16/25—28,400	3/18 —20,400	3/20 —16,000	3/21—Child died								
Premature, 12 hours after birth						Twins								

\* In this column, ♀ indicates female, ♂, male

The reticulocyte count is also increased during pregnancy. Table 9 shows a series of counts in pregnant women. It will be noted that all of these counts were done during the winter months, so that the comparatively slight increase is explained.

TABLE 9—*Reticulocyte Counts on Pregnant Women*

Date	Patient	Month of Pregnancy	Hemoglobin, Per Cent	White Count	Red Count	Reticulocyte Count
Jan 31	O S	Eighth	70	13,000	4,720,000	19,400
Jan 31	A F	Sixth	70	10,000	4,450,000	8,000
Jan 31	R H	Seventh	70	10,500	4,540,000	9,000
Feb 5	M J	Sixth	60	11,000	3,890,000	12,800
Feb 8	M L	Eighth	60	13,000	4,450,000	18,000
Feb 8	J G	Fifth	70	10,000	4,640,000	11,400
Feb 14	K F	Fifth	60	9,000	3,180,000	8,400
Feb 14	S H	Eighth	70	8,000	4,820,000	10,800
Feb 14	K W	Eighth	60	10,000	3,460,000	14,400
March 8	D S	Ninth	65	8,000	3,950,000	15,000
March 7	F J	Eighth	70	8,000	4,340,000	24,000
March 10	B H	Third	80	8,600	5,650,000	21,000

\* The reticulocytes count is somewhat increased during pregnancy.

TABLE 10—*Blood Counts on Patients with Acute and Chronic Infections and Chronic Diseases*

Date	Patient	Type of Infection	Hemoglobin, Per Cent	White Count	Red Count	Reticulocyte Count
11/14	B T	Lobar pneumonia	65	23,000	3,530,000	7,000
1/8	L T	Lobar pneumonia	70	56,800	5,200,000	800
1/12	W R	Lobar pneumonia	70	13,400	4,640,000	4,400
4/1	R B	Lobar pneumonia	70	18,600	4,360,000	10,000
6/18	H R	Bronchopneumonia	75	12,400	4,800,000	1,800
3/29	R C	Bronchopneumonia	75	20,000	4,710,000	800
12/24	M K	Endocarditis	60	10,200	4,510,000	10,000
1/11	C M	Endocarditis	70	10,600	3,820,000	12,000
3/24	B C	Endocarditis	60	15,000	3,950,000	20,000
6/7	B R	Endocarditis	55	8,000	2,900,000	13,000
1/6	G B	Myocarditis	70	7,400	4,690,000	400
1/14	A U	Myocarditis	70	6,500	4,360,000	0
1/26	J C	Typhoid	70	4,200	4,700,000	4,200
2/26	L M	Typhoid	75	5,600	5,120,000	6,000
3/3	J P	Multiple arthritis	80	12,400	5,630,000	1,800
3/5	R C	Multiple arthritis	75	10,000	4,490,000	0
3/2	J M	Multiple arthritis	70	10,200	3,430,000	3,000
12/13	H M	Nephritis, acute	40	7,000	1,790,000	9,000
4/7	H C	Nephritis, acute				7,400
5/28	T H	Nephritis, chronic	85	9,000	5,400,000	16,000
12/11	P B	Catarrhal jaundice	75		4,820,000	0
3/23	H B	Catarrhal jaundice	80		5,100,000	800
4/7	R L	Catarrhal jaundice	80		4,550,000	1,400
6/25	H J	Hanot's cirrhosis	65	5,400	3,500,000	7,400
4/23	F J	Carcinoma of the liver	65	11,400	4,430,000	34,000
2/16	A G	Syphilitic cirrhosis	60	18,000	2,830,000	2,200
4/14	C J	Syphilitic cirrhosis	65	9,800	3,930,000	7,400
2/8	D J	Pelvic infection (acute)	75	13,400	5,190,000	11,200
4/22	M J	Whooping cough	80	21,000	6,530,000	400
1/13	M R	Diabetes	70	8,200	4,120,000	400
10/29	G H	Eczema	80	7,000	4,140,000	6,000

Studies of the reticulocyte count in a series of patients, at the Cincinnati General Hospital, with acute and chronic infections and with chronic diseases showed comparatively little variation from the normal (table 10). When the condition caused anemia, as in the cases of endocarditis, a slight rise in the reticulocyte count occurred. Of interest

also was the high count in the case of carcinoma of the liver, probably due to the metastases of the bone (verified by autopsy)

We were unable to trace any connection between the white count and the reticulocyte count

Reticulocyte counts were done on a group of children at the Preventorium of the Cincinnati Municipal Tuberculosis Sanitarium. There was active tuberculosis in the families of these children, for which reason they had been removed to the preventorium. These children were of both sexes, and ranged in age from 5 to 12 years. None of them had active tuberculosis. The reticulocyte counts were all within normal limits (table 11)

TABLE 11—*Blood Counts in Children in the Tuberculosis Preventorium\**

Patient	Date	Hemoglobin Per Cent	White Count	Red Count	Reticulocyte Count
H F	2/14/27	80	8,000	4,720,000	1,200
I R C	2/14/27	85	9,200	4,200,000	5,400
M O	2/14/27	75	5,400	3,960,000	3,600
P M	2/14/27	80	7,400	4,160,000	6,200
F C	2/14/27	80	8,460	4,020,000	3,400
O B	2/14/27	70	5,600	3,480,000	2,800
T J	2/14/27	75	5,400	3,960,000	3,600
C J	2/14/27	85	5,600	4,120,000	4,200
I W	2/14/27	80	6,800	4,040,000	2,200
L C	2/14/27	80	6,200	4,080,000	6,800
I W	2/14/27	70	7,200	3,440,000	3,400
A L W	2/14/27	85	8,400	4,380,000	4,200
S S	2/14/27	75	4,800	3,960,000	4,400
B S	2/14/27	85	7,800	4,560,000	5,400
A S	2/14/27	90	6,200	4,560,000	5,200
T W	2/14/27	80	7,400	4,200,000	2,200
H C	2/14/27	80	6,600	4,690,000	2,200
M D	2/14/27	85	5,400	4,220,000	1,200
M K	2/14/27	75	11,400	3,880,000	2,000
D B	2/14/27	80	5,800	3,840,000	1,800
C B	2/14/27	75	7,400	3,760,000	4,400
J B	2/14/27	80	5,200	3,970,000	2,000
M D	2/14/27	85	7,600	4,160,000	3,600
E S	2/14/27	95	6,800	5,160,000	4,800
M C	2/14/27	90	7,000	4,350,000	4,800

\* These counts were done on children from the ages of 5 to 12 who were at the Cincinnati Tuberculosis Sanitarium because members of their families had active tuberculosis. There were no active cases in this group.

Counts were done on adults with active tuberculosis, they were all patients at the Cincinnati Municipal Tuberculosis Sanitarium. The results from experiments on twenty-five patients are shown in table 12. The counts were normal in all but three patients who had tuberculosis of the spine, associated diabetes and recent pulmonary hemorrhage, respectively.

*Lead Poisoning*—Lead, as is generally known, causes an increase in the reticulocytes and in the production of stippled cells. Stippled cells are probably reticulocytes which have been affected by the toxic substance lead, in such a way that the granules are much heavier than the granules of normal reticulocytes, so that they can be seen when stained by Wright's stain (or similar stains), without having been vitally stained previously. The term "basophilic degeneration" is well

suted to this condition. It should be remembered, however, that blood which shows stippled cells when stained with Wright's stain will show a much larger number of reticulocytes when stained with brilliant cresyl blue.

The reticulocyte count in lead poisoning and in lead absorption has been made the subject of special study by McCord<sup>11</sup>. He has worked out the details of a test (based on the reticulocyte count) which reveals the degree of lead absorption in workers exposed and permits the institution of preventive measures before actual lead poisoning has taken place. Working in conjunction with McCord to secure, if possible, check results of his test, we ran two series of counts.

TABLE 12—*Blood Counts on Tuberculous Patients*

Patient	Date	Hemo- globin, Per Cent	White Count	Red Count	Reticulocyte Count	
I S	2/16/27	80	6,800	4,240,000	1,000	
R O	2/16/27	85	8,000	4,360,000	2,800	
J St	2/16/27	70	7,100	3,920,000	16,400	Tuberculosis of spine
H O	2/16/27	85	7,800	4,240,000	5,800	No pulmonary tuberculosis
C P	2/16/27	75	9,400	3,960,000	10,800	Tuberculosis plus diabetes
O M	2/16/27	85	5,200	4,920,000	2,200	
W W	2/16/27	90	8,600	5,140,000	2,800	
L M	2/16/27	90	10,200	5,240,000	400	No sputum
					(repeated)	
M S	2/16/27	80	8,800	4,020,000	2,200	
F P	2/16/27	85	7,400	4,380,000	3,600	
A S	2/16/27	70	5,200	3,000,000	1,200	
A St	2/16/27	85	8,200	5,020,000	2,000	Sputum negative
J S	2/16/27	65	11,400	3,480,000	16,200	Recent hemorrhage
D A	2/18/27	80	6,000	4,120,000	1,600	
C S	2/18/27	90	5,800	5,560,000	1,400	
W D	2/18/27	80	6,200	5,060,000	3,600	
E M	2/18/27	95	8,400	1,960,000	1,800	
A J	2/18/27	80	8,000	4,940,000	2,400	
T H	2/18/27	85	9,600	4,160,000	1,000	
J W	2/18/27	70	12,800	3,440,000	600	
H O	2/18/27	80	5,800	4,080,000	1,000	Tuberculosis of spine
L H	2/18/27	60	9,200	3,160,000	1,800	
W L R	2/18/27	85	6,400	4,200,000	1,600	Pneumothorax
L R	2/18/27	80	5,200	4,160,000	2,400	
W Q	2/18/27	70	8,800	3,680,000	3,800	Tuberculosis, laryngitis

\* The counts were done on adult patients with active tuberculosis. All were patients in the Municipal Tuberculosis Sanitarium.

In the first series, table 13, we studied twenty-five normal adults who were working in the offices of lead factories, but who were not directly exposed to the lead hazard. In all except one of these persons (patient 63), the reticulocyte count was normal. The patient in whom the count was not normal was a man who had previously worked in the factory in direct contact with lead.

Table 14 shows the high reticulocyte count in persons working in lead factories, even though they showed no clinical symptoms of lead poisoning.

Lead is not the only heavy metal which causes an increased reticulocyte count. In mercury poisoning the reticulocyte count also goes up, though the rise is not so marked as that seen in lead poisoning. In

11 McCord (footnote 8 second reference)



table 15 are shown the counts in four patients who had taken large doses of corrosive mercuric chloride

Hemorrhage is usually a stimulus to regeneration of the blood, as shown by an increase in the reticulocyte count. In the cases reported in table 16, many reticulocyte counts were done on each patient, but

TABLE 13—*Blood Counts on Normal Adults Working in the Offices of Lead Factories\**

Patient Number	Date	Hemoglobin, Per Cent	White Count	Red Count	Reticulocyte Count
57	11/ 5/26	85	13,200	5,120,000	9,600
58	11/ 5/26	75	9,600	4,760,000	4,800
59	11/ 5/26	80	8,800	4,920,000	3,200
60	11/ 5/26	80	11,800	5,120,000	3,000
61	11/ 5/26	85	13,600	5,240,000	200
62	11/ 5/26	80	8,200	5,160,000	1,000
63	11/ 5/26	85	9,400	5,080,000	18,400
64	11/ 5/26	80	9,200	4,880,000	4,000
66	11/ 5/26	85	14,200	5,280,000	400
67	11/ 5/26	85	8,800	5,360,000	1,800
68	11/ 5/26	75	10,800	4,560,000	7,000
69	11/ 5/26	85	9,400	5,280,000	600
71	11/12/26	90	7,600	5,160,000	600
72	11/12/26	75	11,400	3,960,000	3,800
73	11/12/26	80	12,400	4,240,000	2,600
74	11/12/26	75	11,400	4,040,000	2,200
75	11/12/26	65	12,000	3,760,000	2,400
76	11/12/26	80	10,600	4,360,000	1,400
77	11/12/26	85	9,200	4,600,000	600
78	11/12/26	90	9,200	5,280,000	800
79	11/12/26	85	9,200	4,880,000	9,200
80	11/12/26	90	10,800	5,040,000	1,400
81	11/12/26	95	9,800	5,560,000	800
82	11/12/26	85	8,200	4,820,000	400
83	11/12/26	80	7,800	4,420,000	400

\* These patients had no contact with any form of lead, except one patient, number 63, who had previously worked in the factory and had had an attack of lead poisoning.

TABLE 14—*Blood Counts on Persons Working with Lead*

Date	Patient	Hemo globin per Cent	White Count	Red Count	Reticu- loey te Count	Differential Count				
						Poly morpho- nuclears	Lym- pho- cytes	Mon- onu- clears	To sino phils	Baso phils
11/ 5	W O	60	11,400	3,440,000	32,000	48	47	2	3	0
10/19	J N	80	12,400	1,280,000	12,400	59	37	8	2	0
10/22	J D	70	10,600	3,920,000	70,400	71	46	1	2	0
10/22	L J	70	9,800	3,840,000	22,000	57	39	3	0	1
10/22	C K	85	11,400	5,320,000	44,800	52	45	3	0	0
10/22	W A	65	9,200	3,640,000	61,600	48	48	1	3	0
11/ 5	M D	85	9,400	5,080,000	18,400	61	38	1	0	0
10/22	G A	80	12,400	4,840,000	68,600	49	46	1	4	0

only the maximum reticulocyte count is shown in the table. The time at which the maximum is reached varies with the amount of hemorrhage and the period of time over which it has extended. It is usually reached about five days after the bleeding has stopped. The red cell count then begins to rise and as it approaches normal the reticulocyte count drops.

To a certain degree, the reticulocyte count affords a prognostic index as to whether regeneration of the blood will proceed normally.

after hemorrhage has stopped, or as to whether stimulation to regeneration of the blood, as by transfusion, is needed

In table 17 we show counts in four cases of bleeding duodenal ulcer. These patients were all in the medical service of the Cincinnati General Hospital. All of them presented the classic symptoms of duodenal ulcer, with characteristic roentgen observations. All of them had tarry stools. In two of these patients (W A and E E, table 17), the reticulocyte count did not rise after the bleeding had stopped. One patient, W A, had 1,880,000 red cells with 13,400 reticulocytes. He was given a transfusion of 500 cc of blood with a prompt rise in the

TABLE 15—Counts on Patients with Corrosive Mercuric Chloride Poisoning

Date	Patient	Hemoglobin, Per Cent	White Count	Red Count	Reticulocyte Count
12/23	J J	90	51,600	6,480,000	14,000
1/17	M D	75	120,000	5,510,000	18,000
12/29	E M	80	9,000	4,040,000	3,600
12/20	H K	85	17,000	6,000,000	16,000

TABLE 16—Reticulocyte Counts on Patients After Hemorrhage

Date	Patient	Hemorrhage From	Hemoglobin, Per Cent	White Count	Red Count	Reticulocyte Count *
4/ 5	L M	Duodenal ulcer	40	7,000	2,380,000	64,000
4/27	M T	Epistaxis	30	5,400	2,400,000	57,000
1/25	J M	Ulcerative colitis			2,780,000	80,000
11/26	D H	Tooth extraction	40		2,120,000	64,000
12/ 2	W A	Duodenal ulcer	60	7,000	3,150,000	63,000
12/23	R M	Duodenal ulcer			3,560,000	84,800
12/18	J L	Duodenal ulcer			3,540,000	39,600
1/25	H M	Nose and gums			1,010,000	53,000
2/25	V W	Gastric ulcer			2,230,000	44,000
2/26	G T	Tooth extraction			3,760,000	40,000
4/ 7	J S	Duodenal ulcer			2,950,000	226,000
1/28	C W	Duodenal ulcer			1,770,000	100,000
4/29	E W	Telangiectasis			3,200,000	112,000
10/24	L W	Gastric ulcer	60	4,000	2,900,000	320,000
12/11	P N	Bleeding from gums and bowel			1,320,000	7,200

\* In each of the cases many counts were done, but only the maximum reticulocyte count has been included in the table

reticulocyte count, followed in five days by a marked rise in the red cell count, which was maintained after the reticulocyte count dropped

Another patient, E E, had 2,560,000 red cells with a reticulocyte count of 8,400. After a transfusion of 500 cc, the reticulocyte count rose, followed in six days by a rise in the red cell count, which was maintained until the patient was discharged

In two other cases, R M and L W, the reticulocyte count was found to be high after bleeding had stopped. Accordingly, we advised that transfusion was unnecessary. The reticulocyte count in each instance continued to rise, the red cell count came up and was maintained even after the reticulocyte count had dropped. The figures for the four cases are tabulated in table 17

The amount of blood loss which is necessary to cause a rise in the reticulocyte count evidently varies with the general condition of the patient. Thus, a hemorrhage of 600 cc in healthy man produced no appreciable change in the reticulocyte count (table 18). This man gave 600 cc of blood for a transfusion, without marked change in either the red cell or the reticulocyte count.

TABLE 17—*Reticulocyte Counts on Four Patients with Duodenal Ulcer*

W A, White, Male, Aged 27				E E, White, Male, Aged 43			
Date	Hemoglobin, Per Cent	Red Blood Cells	Reticuloeytes	Date	Hemoglobin, Per Cent	Red Blood Cells	Reticuloeytes
11/26	10	1,880,000	13,400	2/ 3	50	2,056,000	8,400
11/27		Transfusion of 500 cc of blood		2/ 4		Transfusion of 500 cc of blood	
11/28			20,200	2/ 5		2,540,000	88,800
11/30			48,000	2/11		2,680,000	70,000
12/ 1			63,000	2/16		3,390,000	64,000
12/ 2			59,400	3/ 1		3,790,000	34,000
12/ 3	50	3,150,000	53,200	3/ 4	60	3,840,000	14,000
12/ 4			54,000	3/ 8		4,030,000	2,000
12/ 5			54,800	3/16	70	4,100,000	2,400
12/ 7		3,110,000	55,000	3/18		Discharged	
12/ 8			51,000				
12/ 9	65	3,993,000	58,400				
12/11		Discharged					
R M, White, Male, Aged 45				L W, White, Male, Aged 23			
Date	Hemoglobin, Per Cent	Red Blood Cells	Reticuloeytes	Date	Hemoglobin, Per Cent	Red Blood Cells	Reticuloeytes
12/11	40	2,390,000	42,400	10/20	45	2,000,000	109,200
12/18		2,780,000	84,800	10/24	60	2,900,000	320,000
12/23		3,560,000	84,800	10/29	70	3,860,000	160,000
12/28	60	3,680,000	39,200	11/ 5	75	4,130,000	38,400
12/30		Discharged		11/ 7		Discharged	

TABLE 18—*Reticulocyte Count on a Healthy Man Following Hemorrhage\**

Date	Red Count	Reticuloeyte Count
4/27/26	5,200,000	2,000
4/28/26	Hemorrhage of 600 cc of blood	
4/28/26	5,220,000	2,000
4/29/26	5,180,000	5,000
4/30/26	5,200,000	2,000
5/ 1/26	5,030,000	2,200
5/ 2/26	5,240,000	4,800
5/ 4/26	5,400,000	4,200
5/ 7/26	5,360,000	3,000

\* D. H., a healthy man, gave 600 cc of blood for a transfusion. There was no appreciable change in either the red or the reticulocyte count.

On the other hand, a much smaller blood loss caused a definite rise in the reticulocyte count in a tuberculous patient (table 19). J. K., a patient at the Cincinnati Tuberculosis Sanitarium, had a pulmonary hemorrhage of about 200 cc. The hemorrhage produced a rise in the reticulocyte count which reached its maximum seven days after the hemorrhage had occurred.

Patients with blood dyscrasias, other than pernicious anemia, show marked variation in their reticulocyte counts. Single counts on a group of patients with such disorders are shown in table 20.

Patients with familial hemolytic jaundice and with sickle cell anemia show high reticulocyte counts at all times

Patients with hemolytic jaundice (not familial) show some increase in the reticulocyte count, while patients with obstructive jaundice do not. This fact may at times afford a differential diagnostic index of some value. We also noted that the reticulocyte count in acute leukemia

TABLE 19—*The Red and Reticulocyte Counts on a Tuberculous Patient Following Hemorrhage*

Date	Hemoglobin, Per Cent	Red Count	Reticulocyte Count	
1/ 4/27	70	3,880,000	6,200	Six ounce hemorrhage
1/ 5/27		3,960,000	8,600	Sputum bloody
1/ 6/27	70	3,760,000	7,800	Sputum bloody
1/ 7/27		3,610,000	10,400	Sputum blood streaked
1/ 8/27	75	3,700,000	21,000	Sputum blood streaked
1/ 9/27		3,560,000	18,000	Sputum blood streaked
1/10/27	70	3,280,000	22,000	Sputum blood streaked
1/11/27		3,560,000	28,000	Sputum free from blood
1/12/27	70	3,320,000	20,000	Sputum free from blood
1/13/27		3,760,000	16,000	Sputum free from blood
1/14/27	75	3,560,000	11,000	Sputum free from blood
1/16/27		3,560,000	11,000	Sputum free from blood
1/18/27	70	3,600,000	12,000	Sputum free from blood
1/20/27		3,440,000	10,000	Sputum free from blood
1/22/27	70	3,640,000	10,000	Sputum free from blood
1/14/27		3,880,000	10,000	Sputum free from blood
1/26/27	70	3,800,000	7,000	Sputum free from blood
1/28/27		3,840,000	8,000	Sputum free from blood

TABLE 20—*Reticulocyte Counts on Patients with Diseases of the Blood Other than Pernicious Anemia*

Date	Patient	Disease	Hemo- globin, Per Cent	White Count	Red Count	Reticulocyte Count
6/ 1	T S	Malaria			3,400,000	94,000
2/15	J A	Hemophilia	75	8,200	4,430,000	800
12/ 4	D H	Hemophilia	70		4,240,000	4,000
2/11	H P	Hemolytic jaundice	75	7,000	4,850,000	20,000
3/21	M N	Familial jaundice		18,000	4,600,000	220,000
4/23	L S	Purpura			3,960,000	20,000
4/27	M T	Purpura		5,400	2,100,000	57,000
3/14	J M	Lymphatic leukemia (acute)	30	46,000	1,120,000	4,800
4/14	R R	Lymphatic leukemia (chronic)		90,000	3,420,000	8,200
11/29	M S	Myelogenous leukemia (acute)	30	96,800	1,110,000	1,800
12/ 5	J K	Myelogenous leukemia (chronic)	60	80,400	3,030,000	136,000
12/16	L S	Myelogenous leukemia (chronic)	60	510,000	2,010,000	35,600
11/16	C B	Sickle cell anemia		7,200	4,650,000	313,000
3/19	A L	Sickle cell anemia		24,800	2,980,000	416,000
5/17	L B	Von Jaksch's anemia	40	9,800	2,060,000	71,000
11/20	A B	Polycythemia	120		7,840,000	400

is apt to be low. In chronic leukemia the reticulocyte count may offer an aid to prognosis. When the count is high, the patient will probably have a remission, when it is low, there is apt to be a relapse.

Cases of hemophilia show a rise in the reticulocyte count only after hemorrhage.

Cases of polycythemia show a low reticulocyte count.

*Pernicious Anemia*—The value of the reticulocyte count as an index to regeneration of the blood has been so thoroughly attested that it is

now generally accepted. It has been used as a check test to determine the potency of particular kinds of liver extract, or of the variable potency of various batches of extract made by the same process<sup>12</sup>

Table 21 shows the reticulocyte counts on patients with pernicious anemia shortly after admission to the Cincinnati General Hospital before any method of treatment had been instituted. It will be seen that the counts vary greatly, and that before treatment the reticulocyte count and the red cell count do not always stand in direct proportion.

Thus, one patient, G S, showed 3,596,000 red cells with only 6,800 reticulocytes. Another patient, F S, had 1,460,000 red cells, with 256,000 reticulocytes.

What can be asserted is that patients with high reticulocyte counts are soon to have a remission, those with low counts, a relapse unless

TABLE 21—*Reticulocyte Counts on Patients with Pernicious Anemia\**

Date	Patient	Hemoglobin, Per Cent	White Count	Red Count	Reticulocyte Count
4/20	M H	40	1,700	1,648,000	12,000
5/4	L M	70	4,400	2,933,000	11,800
4/20	G S	100	5,250	3,596,000	6,800
5/5	C K	30		1,208,000	1,400
3/24	M K	100		3,008,000	9,000
6/14	C T	30	6,500	1,064,000	12,000
1/11	L Mc	30	4,800	1,330,000	14,600
5/26	M D	70	5,600	3,370,000	36,000
2/24	M K	75	4,400	3,580,000	6,000
3/24	F S	30	4,400	1,460,000	256,000
5/6	M F	60	3,600	2,150,000	8,000
6/16	C C		1,500	1,840,000	23,000
5/5	M B	40	3,600	1,730,000	52,800
5/17	S R			1,500,000	18,000
3/27	D N	30	2,800	780,000	13,600

\* The counts were made immediately after admission to the hospital before any type of treatment was instituted.

treatment is instituted. We have been able to confirm this general hypothesis in the cases studied so far.

Furthermore, if after any method of treatment such as transfusion, heliotherapy, injections of arsenic, etc. the reticulocyte count does not show a rather prompt and marked increase, the probabilities are against the onset of a remission.

While it is true that in some cases an increase in the reticulocyte count (and later in the red cell count) did follow the institution of treatment by one or another of the means noted, it is also true that in no case was the rise so high as it was after the use of liver extract.

It is now a matter of general observation that patients with pernicious anemia respond better to the administration of liver extract than to any other method of treatment. This applies both to blood counts and to general clinical improvement.

<sup>12</sup> Minot, G. R., Murphy, W. P., and Stetson, R. P. *Am. J. M. Sc.* **175**: 581, 1928.

Table 22 gives the maximum reticulocyte counts done on patients with pernicious anemia treated with liver extract

These maximum counts were reached in from seven to nineteen days after the initial dose. The rise in the reticulocyte counts, of course, begins much earlier. Three vials of Lilly's extract were given to each patient daily. So far we have found no case in which the diagnosis of

TABLE 22—*Reticulocyte Counts on Patients with Pernicious Anemia Who Were Given Liver Extract*

Date	Patient	Hemoglobin, Per Cent	White Count	Red Count	Reticulocyte Count
12/21	A B	50	5,000	2,170,000	582,000
1/17	H R	40	1,600	1,480,000	329,000
1/24	H P	40	5,000	1,800,000	240,000
4/16	M P	40	2,550	1,470,000	289,000

\* The patients were given one vial of Lilly's Liver Extract three times daily

TABLE 23—*Reticulocyte Counts on A B, a Patient with Pernicious Anemia, Who Was Given Liver Extract*

Date	Hemoglobin, Per Cent	White Count	Red Count	Reticulocyte Count
12/27/27	40	2,800	1,300,000	7,500
12/14/27			1,430,000	18,400
12/15/27			1,540,000	34,400
12/16/27	50	5,000	1,490,000	42,000
12/17/27			1,730,000	170,000
12/18/27			1,720,000	207,600
12/19/27			1,850,000	363,200
12/20/27			2,090,000	455,000
12/21/27			2,170,000	582,000
12/22/27	60	4,000	2,270,000	489,000
12/23/27			2,500,000	409,000
12/24/27			2,420,000	320,000
12/26/27			2,450,000	118,000
12/27/27			2,390,000	123,000
12/28/27			2,340,000	80,000
12/29/27	65	5,600	2,550,000	40,000
12/30/27			2,670,000	42,000
12/31/27			2,600,000	41,000
1/ 2/28			2,780,000	44,000
1/ 4/28			2,990,000	41,000
1/ 5/28	70	8,000	3,260,000	40,800
1/ 7/28			3,510,000	31,200
1/10/28	75		4,120,000	14,000
1/12/28			4,180,000	11,200
1/14/28			4,350,000	8,400
1/16/28	80		4,600,000	6,400
1/23/28	80	8,000	5,420,000	2,000
2/21/28	90	10,000	5,610,000	3,200
3/22/28	95	7,000	6,010,000	4,000
4/26/28	90	10,000	6,180,000	21,600
5/31/28	95	10,000	6,010,000	5,200

pernicious anemia was certain, in which the patient did not respond to liver extract with a high reticulocyte count, followed by a rise in the red cell count. As the red cell count reaches its maximum, the reticulocyte count drops back to normal.

The rate of increase in counts and the time intervals after the administration of liver extract in pernicious anemia are shown in table 23. The patient in table 23 presented the typical picture of pernicious anemia. The general improvement of his condition kept pace with the improvement in his blood picture.

## COMMENT AND SUMMARY

A clinical method for the accurate counting of the reticulocytes is given. The method is simple, easy to use and enables a worker to count the reticulocytes rapidly and accurately.

We are convinced that the figures for the reticulocyte count as often given are much too high. Such figures as 1 to 1.5 per cent of the red cells in normal persons are incorrect.

Our studies would indicate that the reticulocyte count in normal healthy adults will run from 0.03 to about 0.2 per cent. In other words, the reticulocyte count in the normal healthy adult does not exceed 10,000 per cubic millimeter.

It also seems established that there is a definite increase in the reticulocyte count in healthy persons during the spring months as contrasted with that during the winter months. By our method check counts on the same normal persons ran consistently lower than did counts on the same persons done by other less accurate quantitative methods. The seasonal variation of the count is fairly definite, as shown by various studies.

The higher count during the spring months probably results from the stimulation of the body produced by the increase in ultraviolet rays from the sun at that time. In this connection, it is of interest to note that check counts done at the Taft heliotherapy ward, at the Cincinnati General Hospital, where both natural and artificial rays are used, showed an increase in the reticulocyte count after heliotherapy.

Studies on laboratory animals showed certain definite trends. Counts on rabbits showed great variations, though the counts are much higher than those in human beings.

Cats show lower reticulocyte counts than do human beings. The counts for guinea-pigs, dogs and monkeys approximated those for man.

Physiologic increase in the reticulocyte count is found, as we had previously demonstrated, in the new-born infant. There is also an increase during pregnancy.

Studies on a series of patients with acute and chronic infections and with chronic diseases showed comparatively little variation from the normal unless there was a complicating anemia. We were unable to trace any connection between the white cell count and the reticulocyte count.

Counts made for a group of patients with active pulmonary tuberculosis showed no marked abnormalities. In a group of children at the Preventorium of the Cincinnati Municipal Tuberculosis Sanitarium all without active pulmonary tuberculosis, the counts were within normal limits.

Counts on a group of workers in lead factories, who showed no clinical symptoms of lead poisoning, all ran high. Per contra, counts on persons in the offices of these factories, who were not directly exposed to the lead hazard, were within normal limits.

As is known, lead is not the only heavy metal exposure to which causes a high reticulocyte count. Four cases of corrosive mercuric chloride poisoning are reported, all of the patients showing high counts.

The effect of hemorrhage on the reticulocyte count was studied with particular care. Hemorrhage is, of course, usually a stimulus to regeneration of blood, as shown by the increase in the reticulocyte count. The time at which the maximum reticulocyte count is reached varies with the amount of the hemorrhage. It is normally reached about five days after the bleeding has stopped. The red cell count then begins to rise and as it approaches normal, the reticulocyte count drops.

To a certain extent we feel that the reticulocyte count affords a prognostic index as to whether regeneration of the blood will proceed normally after hemorrhage has stopped, or whether induced stimulation, as by transfusion, is needed. Illustrative cases of bleeding duodenal ulcers, both types, are reported.

Studies were also made on patients with blood dyscrasias other than pernicious anemia. Marked variation in the reticulocyte counts in various conditions was found. Patients with familial hemolytic jaundice and with sickle cell anemia show high reticulocyte counts at all times. Patients with hemolytic jaundice (not familial) show some increase in the reticulocyte count, while patients with obstructive jaundice do not. This may, at times, afford a differential diagnostic index of some value. We found that the reticulocyte count in acute leukemia is apt to be low. In chronic leukemia, the reticulocyte count may offer an aid to prognosis. When the count is high, the patient will probably have a remission, when it is low, there is apt to be a relapse. Cases of hemophilia show a rise in the count only after hemorrhage. Cases of polycythemia show a low reticulocyte count.

The value of the reticulocyte count as an index to the regeneration of blood in pernicious anemia has been so thoroughly attested that it is now generally accepted. It has been used as a check test to determine the potency of particular kinds of liver extract made by the same process. It may also be asserted that patients with high reticulocyte counts are soon to have a remission, those with low counts a relapse (unless treatment is instituted). We were also able to compare results in pernicious anemia in patients treated with liver extract and in others treated with transfusion, arsenic, heliotherapy and other remedies. The general observation that patients with pernicious anemia respond better to liver extract than to any other method of treatment was confirmed.



by these studies. This applies both to red cell counts and to general clinical improvement.

So far we have found no case in which the diagnosis of pernicious anemia was certain in which the patient did not respond to the administration of liver extract with a high reticulocyte count followed by a rise in the red cell count. As the red cell count reaches its maximum, the reticulocyte count drops back to normal.

# THE VARIABILITY OF BLOOD PRESSURE

## II A STUDY OF SYSTOLIC PRESSURE AT FIVE MINUTE INTERVALS

H S DIEHL, M D

AND

H D LEES, M D (Tor)

MINNEAPOLIS

Our recent study of the variability of blood pressure from day to day<sup>1</sup> immediately suggested other questions, such as the amount of time necessary for significant variations of blood pressure to occur and the relation of physical activity to variability of blood pressure. With the hope of throwing some light on these questions we undertook the present study.

### METHODS OF INVESTIGATION

Since our purpose in this study was to observe the variability of blood pressure with the factors of physical activity and long intervals of time kept constant, it was decided to take readings at five minute intervals with the subject inactive throughout. One hundred men students at the University of Minnesota were selected for the study, each student sat quietly at the side of a table, while blood pressure readings were taken at five minute intervals over a period of one hour. The arm band was adjusted at the beginning of the hour and was left in place till the last reading was completed. Mercury instruments and the auscultatory method were utilized throughout. Several physicians of the Health Service staff made the observations, but the same technic was employed by each one. Furthermore, in order to avoid variations due to pressure changes at different times of the day, all readings were taken between 1:30 and 3:30 p. m.

### ANALYSIS OF GROUP STUDIED

The group studied consisted of 100 freshmen of the University of Minnesota unselected except that they were all presumably in normal physical condition. The records of the physical examinations which had been performed on these students at the beginning of the current school year were taken as the basis for judging the students normal.

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\*From the Students' Health Service and the Department of Preventive Medicine, the University of Minnesota.

This study was carried on with the aid of a grant from the Research Fund of the University of Minnesota.

1. Diehl, H. S. The Variability of Blood Pressure. Morning and Evening Studies, Arch. Int. Med. **43**: 835 (June) 1929.

The mean age of the group, at the time of the examination, was  $20.16 \pm 0.14$  years, the mean height,  $68.07 \pm 0.17$  inches, the mean weight,  $136.53 \pm 1.30$  pounds, the mean systolic blood pressure,  $117.53 \pm 0.86$  mm. In a much larger group of freshmen men, who entered the University of Minnesota in 1924, Jackson<sup>2</sup> found a mean age of  $20.078 \pm 0.046$  years, a mean height of  $68.684 \pm 0.042$  inches, a mean weight of  $141.44 \pm 0.29$  pounds, and a mean systolic blood pressure of  $124.28 \pm 0.21$  mm. A comparison of these figures shows that the two groups were practically identical in age and in height, in weight and in mean systolic blood pressure, however, the mean of the group used in the present study was significantly lower. This might be accounted for, at least in part, by the fact that students who were overweight and

TABLE 1—Mean Height of the Several Systolic Readings in Series

	Mean	Difference Between Consecutive Readings
First readings	$118.69 \pm 0.69$ mm	
Second readings	$114.99 \pm 0.66$ mm	$3.70 \pm 0.95$ mm
Third readings	$111.29 \pm 0.70$ mm	$3.70 \pm 0.96$ mm
Fourth readings	$111.72 \pm 0.68$ mm	$0.43 \pm 0.97$ mm
Fifth readings	$110.86 \pm 0.71$ mm	$0.86 \pm 0.98$ mm
Sixth readings	$110.31 \pm 0.72$ mm	$0.55 \pm 1.01$ mm
Seventh readings	$109.49 \pm 0.75$ mm	$0.82 \pm 1.03$ mm
Eighth readings	$108.21 \pm 0.73$ mm	$1.28 \pm 1.03$ mm
Ninth readings	$108.37 \pm 0.71$ mm	$0.16 \pm 1.02$ mm
Tenth readings	$108.84 \pm 0.75$ mm	$0.47 \pm 1.03$ mm
Eleventh readings	$109.19 \pm 0.73$ mm	$0.35 \pm 1.05$ mm
Twelfth readings	$109.48 \pm 0.76$ mm	$0.31 \pm 1.05$ mm
All readings	$110.95 \pm 0.18$ mm	

those with definitely elevated blood pressures were not included in the group. From the point of view of normality, it seems that with the lower systolic pressure the group included in this study is even farther from the borderline than was the group included in Jackson's study, certainly, there is no indication that the present group is not well within normal limits.

#### MEAN HEIGHT OF THE DIFFERENT READINGS IN THE SERIES

The first computation made was the mean of the systolic pressure of the twelve readings taken on each subject, then the mean of these means for the 100 cases was calculated. This mean which is also the mean

2 Jackson, C. M. The Physique of Male Students at the University of Minnesota. A Study in Constitutional Anatomy and Physiology, *Am J Anat* 5:59 (Sept. 15) 1927.

of all readings taken separately, since the same number of readings was taken in each case, was found to be  $110.95 \pm 0.622$  mm.

The means of all the first, second, third, etc., readings, are shown in table 1. The first reading was taken approximately five minutes after the subject sat down at the table, and the subsequent readings at five minute intervals thereafter, so several factors such as rest and allaying apprehension could have contributed to the mean changes in blood pressure that are shown in the table.

The mean of the second readings of the series is  $3.70 \pm 0.95$  mm lower than the mean of the first readings. The actual difference found here is 3.9 times the probable error of the difference, hence, there are approximately 116 chances to 1 that the difference is significant. Between the second and third readings, there is a further decrease of  $3.7 \pm 0.96$  mm, a difference also certainly significant. After the third reading, however, the difference between any two consecutive readings is never large enough to be significant, in fact, between most of the con-

TABLE 2—Highest and Lowest Readings

	Highest	Lowest
First reading	64 cases	3 cases
Second reading	12 cases	2 cases
Third reading	8 cases	4 cases
Fourth reading	4 cases	5 cases
Fifth reading	3 cases	9 cases
Sixth reading	1 case	8 cases
Seventh reading	2 cases	12 cases
Eighth reading	3 cases	21 cases
Ninth reading	0 cases	14 cases
Tenth reading	2 cases	6 cases
Eleventh reading	0 cases	7 cases
Twelfth reading	1 case	9 cases

secutive readings, the actual difference is less than the probable error of the difference. The lowest mean in the series of readings is in the eighth, toward which there is a gradual decrease from the fourth and after which there is a slight but progressive increase to the twelfth. Up to the third reading the drop in mean pressure, as already pointed out, is rapid. From the third to the eighth reading the decrease is gradual, but between these two readings the difference is  $3.08 \pm 1.01$  mm. This difference indicates that although the variation between any two consecutive readings after the third is not significant, there are approximately 26 chances to 1 that the decrease from the third to the eighth reading is significant. The increase between the minimum eighth and the twelfth is  $1.27 \pm 1.05$  mm, a difference certainly not significant.

The relative height of the different readings is shown in another manner in table 2. From this it will be seen that in eighty-four of the 100 cases the first, second or third readings were highest and that in eighty-six of the 100 cases the lowest reading was from the fifth to the twelfth inclusive.

## VARIATION OF BLOOD PRESSURE IN INDIVIDUAL CASES

As a measure of the variation in systolic blood pressure over the twelve readings which were taken on each student, the standard deviation from the mean and the range have been calculated for each case. The distribution of these individual standard deviations, of which the mean is  $5.18 \pm 0.162$  mm, is shown in chart 1A. Our previous study of variation in blood pressure from day to day<sup>1</sup> showed a mean morning standard deviation of  $5.57 \pm 0.167$  mm and a mean evening standard deviation of  $5.86 \pm 0.21$  mm. A comparison of these figures with a mean standard deviation of  $5.18 \pm 0.162$  mm in the present study would

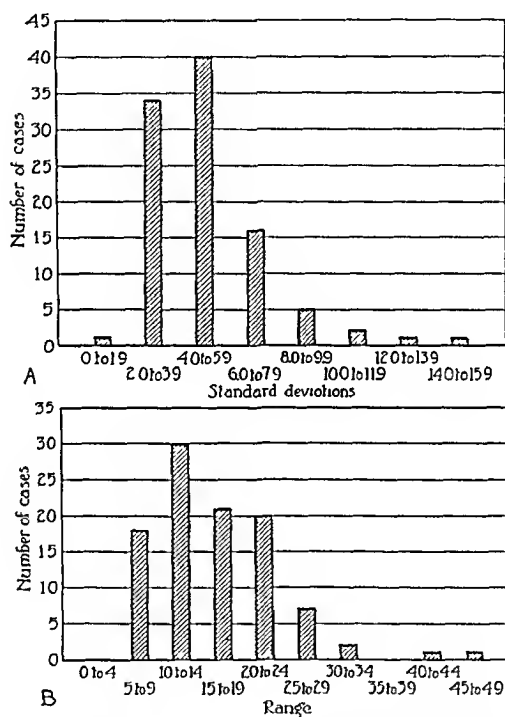


Chart 1—*A*, distribution chart of the standard deviations of the twelve readings taken in each case from the mean pressure in that case. *B*, distribution chart of the range of systolic blood pressure in the individual cases.

seem to indicate that there is as much variability of blood pressure when the subject rests quietly in a chair as there is in the changing activities from day to day. However, we have noted that there is a significant drop in the mean pressure of the group between the first and second and between the second and third readings of the series. This drop in itself would account for a considerable variability from the mean. Omitting these first two readings and then calculating the mean and the standard deviation from the mean for the last ten readings in each case, we find for the 100 cases a mean of the case means of  $109.81 \pm 0.67$  mm and a mean standard deviation of  $3.74 \pm 0.143$  mm. This would indicate that approximately only 28

per cent of the variability is produced by the initial drop in pressure that occurs over the first three readings

Another measure of variability, which is called the range, is the difference between the lowest and highest readings. From a statistical point of view, range is a much less accurate and satisfactory measure of variation than is standard deviation, because when the range is computed only the extremes are taken into consideration all intermediate readings being neglected, whether they are bunched or scattered. Nevertheless, range gives some information and is rather generally understood, hence, it was calculated for the cases in this study. The magnitude of these ranges in systolic blood pressure is shown in a distribution chart (1*B*). The smallest range was 6 mm, the highest 46 mm, the mean,  $16.01 \pm 0.495$  mm, the mode 12 mm and the

TABLE 3—*The Standard Deviations of the Various Readings in the Series*

	Standard Deviation from the Mean
First readings	$10.28 \pm 0.49$ mm
Second readings	$9.73 \pm 0.76$ mm
Third readings	$10.31 \pm 0.49$ mm
Fourth readings	$10.14 \pm 0.48$ mm
Fifth readings	$10.54 \pm 0.50$ mm
Sixth readings	$10.61 \pm 0.51$ mm
Seventh readings	$11.13 \pm 0.53$ mm
Eighth readings	$10.77 \pm 0.51$ mm
Ninth readings	$10.52 \pm 0.50$ mm
Tenth readings	$11.05 \pm 0.52$ mm
Eleventh readings	$10.78 \pm 0.51$ mm
Twelfth readings	$11.22 \pm 0.51$ mm
All readings	$9.22 \pm 0.15$ mm

median, 15 mm. If the first two readings are omitted the mean range was  $11.97 \pm 0.344$  mm.

#### VARIABILITY OF VARIOUS READINGS IN THE SERIES

For the group as a whole, the relative variability of the different readings of the series as measured by the standard deviation from the mean is shown in table 3. As will be seen from this table the standard deviation from the mean is practically the same for all of the readings in the series, in fact between the lowest standard deviation (the second) and the highest (the twelfth) the difference is only  $1.49 \pm 0.71$  mm. In other words there is only about one chance in five that even this maximum difference is not accidental. Hence although as pointed out in the previous paragraph the mean for the successive readings shows a definite downward tendency there is no significant difference in the reliability of any of the readings of the series.

## VARIABILITY AT DIFFERENT LEVELS OF BLOOD PRESSURE

The relation of the mean blood pressures of the group to the variability which these pressures exhibited over the series of twelve readings was calculated by computing the coefficient of correlation between the individual mean pressures and the standard deviations of the twelve readings in each case from the case mean. As this coefficient of correlation was found to be  $0.0746 \pm 0.067$ , we can say that there is no correlation in this group between the height of the blood pressure and its variability. Table 4 shows the distribution of the data from which the coefficient of correlation was computed. In our previous study of variability of blood pressure<sup>1</sup> we likewise failed to find any significant correlation between the height of the pressure and its variability. In the present group, however, this lack of any significant correlation is still more surprising because the mean pressure of many of these students was low enough to be rather close to the lower physio-

TABLE 4—*Distribution Chart of Mean Pressure and Standard Deviation*

Mean Pressure	Standard Deviation															Total
	1 to 19	2 to 29	3 to 39	4 to 49	5 to 59	6 to 69	7 to 79	8 to 89	9 to 99	10 to 109	11 to 119	12 to 129	13 to 139	14 to 149		
90-94		1		2											3	
95-99		2	1		6	2	1								12	
100-104		2	3	6	3		1								15	
105-109		2	3	1	5	2	2	1				1			17	
110-114			5	4	2	3		1		1	1				17	
115-119	1	2	4	2	2	2	1	2	1						17	
120-124		1	4	3	2	2									12	
125-129			3		2										5	
130-134			1											1	2	
Total	1	10	24	18	22	11	5	4	1	1	1	1	0	1	100	

logic limits of blood pressure in fact 15 of the 100 cases showed a mean systolic pressure of less than 100.

## GRAPHS OF REPRESENTATIVE CASES

In chart 2, twelve consecutive blood pressure readings in eight representative cases are portrayed graphically. In case 1 there is little variation, although a slight tendency for the pressure to increase during the hour. Case 2 shows first a gradual increase in pressure and then a considerable variability, there being a drop of 14 mm. in one five minute interval. Cases 3 and 4 show slight variation with little increase or decrease from the mean. Cases 5, 6 and 7 represent the most frequent type of curve, showing a decided decrease in pressure over the first four or five readings with relatively little variation after that. Case 8 presents a unique curve but is included because it shows first a decrease of 4 mm. followed by a gradual increase of systolic pressure from 118 to 160 mm. in fifty-five minutes. It is interesting to note also that the boy who presented this remarkable sequence of blood pressure

readings was brilliant and highly emotional and was arrested for burglary a few days after the readings were taken

#### COMMENT

In a previous study, the variation in blood pressure in 100 cases from day to day for six consecutive days was found to show in the morning a mean standard deviation of  $5.57 \pm 0.167$  mm and a mean range of  $16.29 \pm 0.486$  mm and in the evening, a mean standard

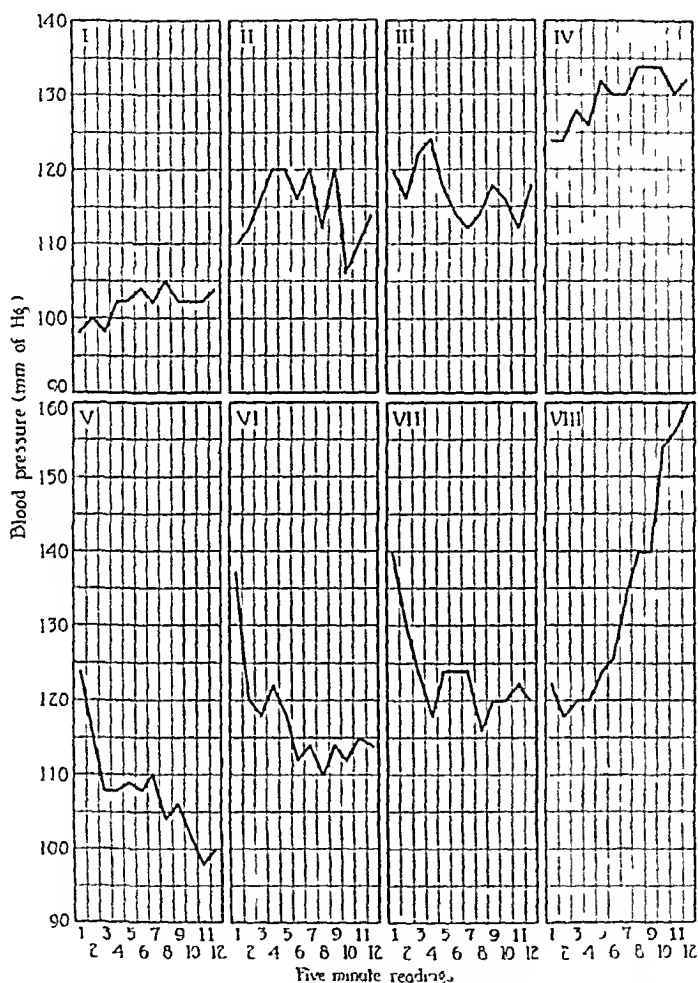


Chart 2—Graphs of the systolic blood pressure in representative cases with readings taken at five minute intervals

deviation of  $5.86 \pm 0.21$  mm and a mean range of  $17.86 \pm 0.616$  mm. The morning readings were taken between rising and breakfast and the evening readings just before dinner. Throughout the day the students carried out their usual activities, no attempt being made to control or limit them. In the present study the subjects sat quietly at a table throughout the series of twelve readings and all readings were taken at approximately the same time in the afternoon. Under these controlled conditions, the mean standard deviation for the twelve readings



was  $5.18 \pm 0.162$  mm, and the mean range,  $16.01 \pm 0.495$  mm. If the first two readings are omitted from the computations, the mean standard deviation was  $3.74 \pm 0.143$  mm and the mean range,  $11.97 \pm 3.44$  mm. The mean pressure for all readings taken on the previous group was  $119.76 \pm 0.244$  mm, while the mean pressure for the present group is  $110.95 \pm 0.18$  mm. From this it would appear that controlled conditions affect the elevation of blood pressure much more than its variability. A similar conclusion could be drawn from the fact that in the present study there is a decrease in the mean pressure of the successive readings, but no significant changes in their standard deviations.

Although the mean of the 1,200 readings taken on this group was  $110.95 \pm 0.18$  mm, the mean systolic pressure of the same students on entrance examinations a few months previously was  $117.52 \pm 0.86$  mm. The students naturally were more apprehensive during the entrance examinations than they were during the present study, and at that time only two blood pressure readings were taken on each student. Consequently, the readings on entrance examinations would correspond more closely to the first readings of this series, the mean of which was  $118.69 \pm 0.69$  mm. This relationship of the mean pressure in the present study and the mean pressure on entrance examinations bears out the suggestion which was made in a previous paper,<sup>3</sup> that most of the high blood pressure readings that are recorded at the time of the physical examinations performed when the students enter college are due to transient elevations of blood pressure and do not represent a true picture of the usual blood pressure values of the group.

The lowest mean pressure in the series is found in the eighth reading, but no significant difference between successive readings is found after the third reading, furthermore, 84 per cent of the cases showed the highest pressure on the first, second or third readings. From this it would seem that if one takes four blood pressure readings at five minute intervals, there is little probability of obtaining any lower pressure or any less variability even though a considerably greater number of readings is taken.

#### SUMMARY

1 Blood pressure readings for 100 healthy men students in the freshman class of the University of Minnesota were taken every five minutes for one hour.

2 The mean systolic pressure of all readings was  $110.95 \pm 0.18$  mm.

3 The mean of the standard deviations of the individual cases was  $5.18 \pm 0.162$  mm, and the mean range,  $16.01 \pm 0.495$  mm.

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3 Diehl H. S., and Sutherland, K. H. Systolic Blood Pressures of Young Men, *Arch Int Med* **36** 151 (Aug) 1925.

4 The mean of the first three readings of the series shows significant decreases between consecutive readings, but after the third reading the difference between any two consecutive readings is less than the probable error of the difference. There is, however, a gradual decrease in the mean of the series until the eighth reading, which is the lowest point reached. From the eighth to the twelfth reading there is a slight, though not significant, increase in mean pressures.

5 The standard deviations of the various readings of the series show no significant differences, indicating that although in the series of readings the pressure decreases, the variability remains constant.

6 There is no relationship in this series between the level of the systolic pressure and its variability.

# SUGAR TOLERANCE IN ARTHRITIS

## II ARTHRITIS OF THE MENOPAUSE<sup>†</sup>

BENJAMIN H ARCHER, M D

NEW YORK

In the previous communication the question of sugar tolerance in chronic infectious arthritis was discussed. In the series of cases reported no evidence was found of a diminished sugar tolerance. Furthermore the results of the study tended to prove that the tolerance for dextrose does not vary with the severity of the arthritic process, and also showed that foci of infection apparently have no specific effect on the sugar storage mechanism.

It is intended, in the present study, to present the data for a parallel series of cases of the menopause type of degenerative arthritis in which the sugar tolerance test was done coincidentally with the tests in the aforementioned series of infectious cases. As previously described,<sup>1</sup> the arthritis of the menopause occurs chiefly in obese, middle-aged women at the time of or just after the menopause, and is characterized by the presence of grating knee joints and Heberden's nodes. The evidence at hand points to a noninfectious origin.

As seen in table 1, all of the patients in this series were women. Although the menopause syndrome has been found occasionally in men, associated with signs of endocrine failure, the typical case occurs in women following the climacteric. The average age was 56½ years. The average weight was 172½ pounds (78.2 Kg), and the average height 5 feet 2½ inches (158.8 cm). The normal weight for women of this age and height is 141 pounds (64 Kg). The women in this group were 31½ pounds (14.3 Kg) overweight. The women in the series of infectious cases were slightly underweight. It is also of interest to note that the average age of women with the arthritis of the menopause is 17 years in advance of the average age of those in the infectious group. These observations are consistent with those made formerly.<sup>2</sup>

The mean systolic blood pressure in this series was 146 mm and the mean diastolic pressure 81 mm. Six of the patients had a systolic pressure of 150 or more, and five of these had a diastolic pressure of more

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<sup>†</sup> Submitted for publication, Dec 5, 1928.

From the Cornell Clinic and the Department of Medicine of Cornell University Medical College.

1 Cecil, R. L., and Archer, B. H. Arthritis of the Menopause, J. A. M. A. 84:75 (Jan. 10) 1925.

2 Cecil, R. L., and Archer, B. H. Classification and Treatment of Chronic Arthritis, J. A. M. A. 87:741 (Sept. 4) 1926.

than 90. A marked degree of obesity was present in nine cases or in nearly half of the series. In four members of this group, the obesity was associated with hypertension. Practically all of these women had passed the menopause with its concomitant endocrine changes. It has been shown that obesity,<sup>3</sup> hypertension<sup>4</sup> and endocrine dyscrasia<sup>5</sup> may influence the sugar tolerance curve. A study of the foregoing data shows that these factors were operative in this series of cases.

## METHOD

The Hamman and Hirschman<sup>6</sup> method of conducting the test for sugar tolerance was used throughout this study. It consists of the oral administration of 100 Gm of dextrose while the patient is fasting. Samples of blood and urine are collected one-half, one, two and three hours, respectively, after the ingestion of

TABLE 1—Clinical Data on Twenty Cases of Arthritis of the Menopause

Number	Name	Age	Weight, Pounds	Height, Inches	Average Weight Pounds	Blood Pressure	Associated Conditions
1	H L	51	216½	63½	141	144/ 86	Obesity
2	C W	61	188½	60	135	180/110	Obesity, hypertension
3	G S	59	147½	68½	138	126/ 60	
4	M S	42	151	66	129	110/ 70	
5	N B	60	151	62½	139	120/ 65	
6	J G	49	152½	66½	149	170/100	Hypertension
7	R K	63	185	61½	135	150/ 78	Obesity
8	R S	49	214½	59	131	140/ 70	Obesity
9	A D	52	185	63	141	114/ 74	Obesity
10	E T	69	186	65	148	210/100	Obesity, hypertension
11	O H	55	150	63	141	146/ 80	
12	A S	53	132	64	144	130/ 80	
13	L D	43	169	63	138	120/ 70	
14	M E	64	189	61¼	135	192/102	Hypertension, obesity
15	C McO	60	115	60½	135	130/ 60	
16	C C	63	197	62	138	132/ 72	Obesity
17	L W	68	178	63	141	146/ 80	
18	M G	56	142	62	138	110/ 80	
19	G W	53	165½	63¼	141	140/ 82	Hypothyroidism
20	H R	60	229½	64	144	174/100	Obesity, hypertension

the sugar. The test is preceded by the drawing of the blood during fasting and the collection of a specimen of urine.

The quantitative determination of the blood sugar was made by the Benedict<sup>7</sup> modification of the Lewis and Benedict<sup>8</sup> method. The tests were performed in

3 John, H. J. The Relationship of Obesity to Carbohydrate Metabolism. *Am J M Sc* **173** 184 (Feb.) 1927. Allison, R. S. Carbohydrate Tolerance in Overweight and Obesity, *Lancet* **1** 537 (March 12) 1927.

4 O'Hare, J. P. Glucose Tolerance Test in Chronic Vascular Hypertension. *Am J M Sc* **159** 369 (March) 1920. Herrick, W. W. Hypertension and Hyperglycemia, *J A M A* **81** 1942 (Dec 8) 1923.

5 Janney, N., and Isaacson, J. The Blood Sugar and Thyroid and Other Endocrine Diseases. The Significance of Hypoglycemia and the Delayed Blood Sugar Curve, *Arch Int Med* **22** 160 (Aug.) 1918.

6 Hamman, L., and Hirschman, F. L. Alimentary Hyperglycemia and Glycosuria as a Test for Sugar Tolerance, *Arch Int Med* **20** 761 (Nov.) 1917.

7 Benedict, S. R. Note on the Determination of Blood Sugar by the Modified Picric Acid Method, *J Biol Chem* **37** 503, 1919.

8 Lewis, R., and Benedict, S. A Method for the Estimation of Sugar in Small Quantities of Blood, *J Biol Chem* **20** 61, 1915.

the Cornell Clinical Pathological Laboratory under the supervision of Dr Thro. It should be noted that the procedures followed in this series were the same as those employed by Pemberton and Foster,<sup>9</sup> and by me in the study of the infectious cases

## COMMENT

The results of the tests are shown in table 2

The mean level during fasting for this series was 0.111 per cent. One-half hour after the administration of the dextrose, the mean reading for the group was 0.166 per cent. At the end of an hour the figure rose to 0.167 per cent. After two hours it was 0.138 per cent, and at the end of three hours the curve dropped to 0.114 per cent. The highest level during fasting in any one case in the series was 0.125 per

TABLE 2—*Observations on the Blood and Urine*

Number	Blood Sugar, in Milligrams per Hundred Cubic Centimeters					Urine Sugar				
	Fasting	½ Hour	1 Hour	2 Hours	3 Hours	First Test	Second Test	Third Test	Fourth Test	Fifth Test
1	125	166	187	136		Negative	Negative	Negative	Negative	Negative
2	100	166	166	115	115	Negative	Negative	Negative	Negative	Negative
3	115	150	136	115		Negative	Negative		Negative	Negative
4	115	166	150	115	115	Negative	Negative	Negative	Negative	Negative
5	107	150	166	166	136	Negative	Negative	Negative	Negative	Negative
6	115	136	166	125	100	Negative	Negative	Negative	Negative	Negative
7	115	166	200	187	125		Negative	Negative		Negative
8	100	166	166	133	100	Negative	Negative	Negative	Negative	Negative
9	125	230	187	166		Negative	Negative	Negative	Negative	Negative
10	100	150	136	136	115	Negative	Negative	Negative	Negative	Negative
11	115	166	166	150	125	Negative	Negative	++	++	++
12	100	150	150	136	115	Negative	Negative	Negative	Negative	Negative
13	115	150	150	150		Negative	Negative	Negative		
14	115	187	230	187	125	Negative	Negative	Negative	++	Negative
15	115	166	187	136	115	Negative	Negative	Negative	Negative	Negative
16	115	187	166	150	100		Negative	++		++
17	125	187	214	136	125	Negative	Negative	Negative	Negative	Negative
18	107	166	150	125	100	Negative	Negative	Negative	Negative	Negative
19	100	136	125	125	115	Negative	Negative	Negative	Negative	Negative
20	90	125	150	107	95	Negative	Negative	Negative	Negative	Negative

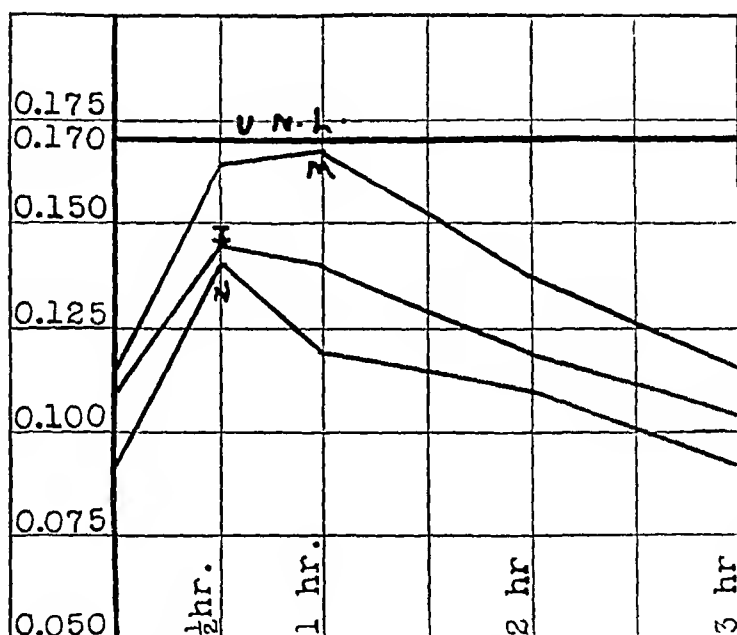
cent. The lowest level was 0.090 per cent. The maximum concentration in any one case after the ingestion of dextrose was 0.23 per cent. The minimum response was 0.136 per cent. Glycosuria was present in only three cases.

Considered by the criteria adopted in the previous study, a post-prandial reading of blood sugar of 0.17 per cent or more was taken to be an evidence of a diminished sugar tolerance. As seen in table 2, seven cases, or 35 per cent of the series, fall into this category. The failure of the tolerance curve to return to the fasting level three hours after the administration of dextrose is conceded by practically all observers to be an evidence of a diminished power to assimilate dextrose.

9 Pemberton, R., and Foster, G. Studies on Arthritis in the Army based on Four Hundred Cases. III. Studies on the Nitrogen, Total Fat and Cholesterol of the Fasting Blood, Renal Function, Blood Sugar and Sugar Tolerance, *Arch Int Med* 25:243 (March) 1920.

Seven, or 35 per cent of the group, had a normal tolerance peak but the curve failed to return to the predextrose level in three hours. Only two cases, or 10 per cent of the series, showed both a maximum concentration of more than 0.17 per cent and a failure of the curve to return to the predextrose level in three hours.

If all cases in which a derangement of the sugar tolerance was present are included, it is found that fourteen cases, or 70 per cent of this series, show a diminished tolerance for dextrose. This result is in marked contrast with the parallel group of infectious cases in which only 15 per cent of the series showed a diminished power to assimilate dextrose. The observations are also abnormal as compared with the



Average curve for the menopause series contrasted with the average curve for the infectious cases, and with the curve for the normal subjects as given by Gray. *N* represents the normal curve, *I* the curve for the infectious cases, *M*, the curve for the menopause cases, and *U.N.L.*, the upper normal limit as established by Gray.

figures reported by Gray<sup>10</sup> who noted departures from the average tolerance curve in 13 per cent of a series of 300 clinically normal subjects.

In the chart is seen the mean curve of the entire series as contrasted with the mean curves of the series of infectious cases and of Gray's series of 300 normal subjects.

The average predextrose level in the menopause cases (0.111 per cent) was the highest of the three groups. The average blood sugar concentration one-half hour after the administration of the test load, was 0.163 per cent, a postdextrose rise of 0.052 per cent. After one hour

10 Gray, H. Blood Sugar Standards, Arch. Int. Med. 31:241 (Feb.) 1923.

the average maximum concentration (0.167 per cent) was reached. This was a postprandial rise of 0.056 per cent which was above the normal maximum postdextrose rise (0.05 per cent) as determined by Gray. It is interesting to note that the average maximum blood sugar concentration in the menopause group was reached in one hour, while in the infectious cases and in the normal group tested by Gray the greatest concentration was attained in one-half hour. This observation is consistent with that of Spence<sup>11</sup> who found a tendency in older subjects to have a higher and a more prolonged curve. This may be the explanation for the fact that the menopause curve fails to return to the predextrose level in three hours, the average reading at that time being 0.114 per cent, and therefore 0.003 per cent higher than the level maintained during fasting.

A comparison of the sugar tolerance between the menopause and the infectious cases shows that the average maximum blood-sugar concentration in the former group was 0.167 per cent, while in the latter it was only 0.146 per cent. Furthermore, the postdextrose rise in the menopause series was 0.056 per cent while in the infectious group it was only 0.038 per cent. In the infectious cases there was a return to the predextrose level after three hours, while in the menopause series the mean curve at the end of the test was above the level maintained during fasting. Finally, while the average predextrose reading of the menopause cases was only 0.003 per cent higher than the mean predextrose level of the infectious group, three hours after the feeding of dextrose the menopause curve is 0.012 per cent higher than the mean reading for the infectious cases. It is interesting to note that patients with arthritis of the menopause, which is believed by most observers<sup>12</sup> to be of noninfectious origin, show a diminished sugar tolerance while those with arthritis of the chronic infectious type fail to show this deviation from the normal.

There are operative in this series of menopause cases other factors than the disease of the joints which should be given due consideration in the interpretation of the results obtained. It has been shown that obesity, hypertension and endocrine dyscrasia may influence the sugar tolerance curve. As already indicated, five of the patients had a definite hypertension. Three of these, or 60 per cent, showed a diminished tolerance for dextrose. The clinical diagnosis of obesity was made in nine cases of this group. Seven of these, or 78 per cent, showed a lowered sugar tolerance. In four, the obesity was associated with hypertension. Of this group, three, or 75 per cent, showed a diminished

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11 Spence, J. C. Some Observations on Sugar Tolerance, with Special Reference to Variations found at Different Ages, *Quart. J. Med.* **14** 314 (July) 1921.

12 Symposium on Climacteric Arthritis, *Proc. Roy. Soc. Med.* **20** 511 (Feb) 1927.

tolerance for dextrose. While the degree of endocrine disturbance present in this series of patients cannot be accurately determined, it may be assumed that in all of those who are either passing through or have passed the menopause, a definite endocrine dyscrasia is present. To what extent this influences the results obtained, it is impossible to say.

In this series of fourteen patients with arthritis of the menopause who show a diminished sugar tolerance, ten, or 71 per cent, have as associated conditions, hypertension, obesity or both. All fourteen are affected by the endocrine changes of the menopause. As it has been shown that any one of the factors mentioned may cause a diminished tolerance for dextrose, one cannot draw the conclusion that the diminished sugar tolerance found in the present series of cases is due to the chronic disease of the joints that is present.

#### CONCLUSIONS

1. In a series of twenty typical cases of arthritis of the menopause fourteen, or 70 per cent, show a diminished sugar tolerance. This is in marked contrast to the parallel series of infectious cases in which only three or 15 per cent, showed a lowered tolerance for dextrose.

2. Ten of the fourteen cases showing a lowered tolerance for dextrose have, as associated conditions, hypertension or obesity or both.

3. As it has been demonstrated that either hypertension or obesity may cause a lowering of the sugar tolerance, it is impossible to say that the diminished sugar tolerance found in this series of cases is due to the chronic disease of the joints that is present.



# INORGANIC SERUM SULPHATES IN RENAL INSUFFICIENCY

A COMPARATIVE STUDY OF BLOOD UREA AND CREATININE  
THE EFFECT OF DIURESIS ON SERUM SULPHATES\*

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The paucity of knowledge concerning sulphate constituents of the blood probably is due to the fact that methods have not been available which could be used because the quantities of blood required for gravimetric or volumetric procedures were impracticable. During the last few years, however, several so-called microchemical methods have been described. Noteworthy of these methods are the nephelometric method of Denis,<sup>1</sup> the colorimetric method of Hubbard,<sup>2</sup> the gravimetric method of Loeb and Benedict<sup>3</sup> and the volumetric method of White.<sup>4</sup> The latter is a modification of Fiske's<sup>5</sup> volumetric method for determining urinary sulphates.

In recent years several investigators have determined blood sulphates in normal and in various pathologic conditions. Normal sulphate values do not compare very well, as is shown in table 1. One of the factors which might cause disparity of results is that a different method was used in each instance.

Blood sulphates have been as carefully studied in renal disease as in any pathologic condition. In 1921,<sup>6</sup> Denis reported results which indi-

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\* Work done under supervision of Dr N M Keith, Division of Medicine, The Mayo Clinic

1 Denis, W. Sulfates in Blood, *J Biol Chem* **49** 311, 1921. Denis, W, and Reed, Lucille. Methods for the Determination of Some of the Nonprotein Sulfur Compounds of Blood, *J Biol Chem* **71** 191, 1926. Denis, W, and Reed Lucille. A Study of the Influence of Kidney Function on the Concentration of Certain Nonprotein Sulfur Compounds in the Blood, *J Biol Chem* **73** 41, 1927.

2 Hubbard, R S. A Colorimetric Method for the Determination of Sulphate in Serum, *J Biol Chem* **74** 5, 1927.

3 Loeb, R F, and Benedict, Ethel M. Inorganic Sulphates in Human Blood, *J Clin Investigation* **4** 33, 1927.

4 White, H L. Studies on Renal Tubule Function. III. Observations on the Excretion of Sulphate with a Modified Technique for the Determination of Inorganic Sulphate in Blood or Plasma, *Am J Physiol* **65** 537, 1923.

5 Fiske, C H. The Determination of Inorganic Sulfate, Total Sulfate, and Total Sulfur in Urine by the Benzidine Method, *J Biol Chem* **47** 59, 1921.

6 Denis (footnote 1, first reference)

cated that the inorganic sulphates were retained in cases of renal insufficiency, and that this retention had some relation to the retention of nonprotein nitrogen. In 1928, this same observer<sup>7</sup> made a second study in a few cases of nephritis and concluded, "There does not appear to be any direct relation between the retention of nonprotein nitrogen and inorganic sulphate." Loeb and Benedict studied sulphate retention in cardiac and renal disease, and concluded that there was a relationship between retention of sulphate, urea and creatinine.

The objects of the following study were (1) to determine whether in different types of renal insufficiency inorganic sulphates are retained, (2) if they are retained, to find out whether there is any relationship between this retention and the retention of urea and creatinine, and (3) to study the effect of diuresis on serum sulphates.

TABLE 1—*Comparisons of Normal Inorganic Sulphates*

Case	Sulphates in Each 100 Cc of Plasma (Denis)*	Sulphates in Each 100 Cc of Serum (Loeb and Benedict)	Sulphates in Each 100 Cc of Serum (Results by the Author)
1	16	27	0.5
2	19	34	0.6
3	14	41	1.1
4	16	48	1.1
5	13	21	1.2
6	0.9	34	1.
7	0.7	34	1.3
8	14	34	1.4
9	10	41	1.4
10		41	1.4
11		24	1.5
12		34	1.5
13		27	

\* Denis' original figures were in terms of sulphur. In this tabulation her figures are expressed in terms of sulphate.

The general types of cases studied may be enumerated as follows: renal insufficiency secondary to generalized vascular disease, 29, acute and chronic diffuse glomerulonephritis, 11, chronic nephrosis, 5, chronic pyelonephritis, 2, renal insufficiency associated with hypertrophy of the prostate, 2, renal lithiasis, 1, and acute renal insufficiency following an operation, 1.

The samples of blood for the determinations were obtained from patients who were in the hospital, and were drawn from two to three hours after the morning meal. In most instances, the patients had been in the hospital for two or more days and were fairly well established on a low protein, low salt diet with a liberal fluid intake of 2,000 cc or more daily. The blood was allowed to clot and then the serum was separated by centrifugating. Samples for the determination of urea

7 Denis, W., Herrmann, G. R., and Reed, Lucille. The Nonprotein Sulphur of the Blood in Certain Pathological Conditions, *Arch. Int. Med.* **41**: 385 (March) 1928.

and creatinine were drawn at the same time as those for the sulphates. Inorganic serum sulphates were determined by a colorimetric method, the principle of which was first described by Hubbard.<sup>8</sup> Creatinine in whole blood was determined by the method of Folin and Wu,<sup>9</sup> and urea by the method of van Slyke and Cullen.<sup>10</sup> All determinations of sulphates were done in duplicate. Normal values for serum sulphate range from 1.5 to 0.5 mg. in each 100 cc. of serum (table 1). It has been observed that values for serum sulphate in patients who are in the hospital for causes other than renal disorders and in whom there is no suspicion of renal disease, are higher than the values shown in table 1. Values for serum sulphate in ten patients who were in the hospital, together with the clinical diagnosis, are given in table 2. This table is offered in the hope that it will illustrate that values for inorganic serum sulphate may be much higher than the normal values given in table 1 without any known reason.

TABLE 2—*Inorganic Serum Sulphates in Hospitalized Patients Who Did Not Show Evidence of Renal Disease*

Case	Diagnosis	Inorganic Serum Sulphate in Mg. for Each 100 Cc.
1	Duodenal ulcer	3.0
2	Diabetes mellitus	3.1
3	Diabetes mellitus	2.2
4	Hypoglycemia	1.9
5	Carcinoma stomach	2.3
6	Carcinoma stomach	2.0
7	Pulmonary tuberculosis	3.0
8	Ovarian tumor	2.5
9	Bleeding hemorrhoids, secondary anemia	2.1
10	Neurasthenia	2.5

For the sake of clearness, the results are divided into three arbitrary groups. The results recorded in table 3 were obtained in cases in which the urea content of the whole blood was more than 100 mg. in each 100 cc., in table 4, in cases in which the urea content of the whole blood was from 70 to 100 mg. in each 100 cc., in table 5, in the cases in which the urea content of the whole blood was from 40 to 70 mg. in each 100 cc.

The patients who made up group 1 (table 3) were in the terminal stages of different types of renal and vascular disease. Case 14, in which the highest sulphate value was found, was an instance of the

8 Full details of the author's experience with this method are included in Wakefield, E. G. The Colorimetric Determination of Total and Inorganic Sulphates in Blood Serum, Urine and Other Body Fluids, *J. Biol. Chem.* **81** 713 (March) 1929.

9 Folin, Otto, and Wu, Hsien. A System of Blood Analysis, *J. Biol. Chem.* **38** 81, 1919.

10 Van Slyke, D. D., and Cullen, G. E. A Permanent Preparation of Urase and Its Use in the Determination of Urea, *J. Biol. Chem.* **19** 211, 1914.

so-called malignant hypertension of Keith and Wagener<sup>11</sup> Renal insufficiency developed, and the patient died from uremia. It is well to point out the fact that the values for inorganic sulphates in this group probably are technically a little high as the phosphates were not removed from the trichloroacetic acid filtrate. The important thing is that without a single exception, inorganic sulphates are increased. There is no strict correlation between the increase of sulphates and retention

TABLE 3—*Comparison of Retention of Urea and Creatinine with the Quantity of Inorganic Serum Sulphates in Uremia*

Case	Urea, Mg in Each 100 Cc of Whole Blood	Creatinine, Mg in Each 100 Cc of Whole Blood	Inorganic Sulphate, Mg Sulphate in Each 100 Cc of Blood Serum
1	106	4.1	9.5
2	113	6.8	8.1
3	116	5.7	8.2
4	117	6.5	6.5
5	125	5.0	8.4
6	127	5.0	7.2
7	128	7.0	5.0
8	155	7.6	11.6
9	165	8.0	12.0
10	209	3.7	35.8
11	212	9.0	18.0
12	256	11.2	23.2
13	258	11.4	15.0
14	263	4.7	6.2
15	274	12.2	29.8
16	328	11.0	29.0

TABLE 4—*Comparison of Retention of Urea and Creatinine with the Quantity of Inorganic Serum Sulphates in Cases in Which the Values for Blood Urea Were Between 70 and 100 mg in Each 100 cc*

Case	Urea Mg in Each 100 Cc of Whole Blood	Creatinine, Mg in Each 100 Cc of Whole Blood	Inorganic Sulphates, Mg Sulphate in Each 100 Cc of Blood Serum
1	70	2.4	4.3
2	71	2.6	9.8
3	74	2.7	2.7
4	77	3.3	9.8
5	78	5.5	4.7
6	83	3.5	5.8
7	89	5.2	8.2
8	90	4.5	6.8
9	93	3.5	7.5
10	98	5.8	8.1

of urea and of creatinine. For example, one might point out the fact that the value of serum sulphate in case 10 is practically twice that in case 11, whereas there is a difference of 3 mg in each 100 cc in the values of blood urea in the same two cases. On comparison of the

<sup>11</sup> Keith, N. M., Wagener, H. P. and Kernohan, J. W. The Syndrome of Malignant Hypertension, *Arch. Int. Med.* **41**: 141 (Jan.) 1928. Wagener, H. P. and Keith, N. M. Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, *ibid.* **34**: 374 (Sept.) 1924.

values of creatinine in these two cases, it is seen that the reverse is true, that is, in case 11 twice as much creatinine is retained as in case 10

In group 2 (table 4) there is wider variation in the results. The highest values for sulphate are in cases 2 and 4, between which there is a difference of 6 mg of urea in each 100 cc of blood. It happens that the first and last cases have the lowest and the highest values for urea and creatinine, respectively, but between cases 9 and 10 there is a difference of 2.3 mg in the blood creatinine in each 100 cc, with a difference of only 5 mg in the blood urea in each 100 cc and a difference of 0.6 mg in each 100 cc in the values for serum sulphate.

The values for inorganic sulphates in group 3 (table 5) vary more than in either of the other two groups. Practically the same can be

TABLE 5—*Comparison of Retention of Urea and Creatinine with Quantity of Inorganic Serum Sulphates in Cases in Which the Values for Blood Urea Were Between 40 and 70 mg in Each 100 cc*

Case	Urea, Mg in Each 100 Cc of Whole Blood	Creatinine, Mg in Each 100 Cc of Whole Blood	Inorganic Sulphates, Mg Sulphate in Each 100 Cc of Blood Serum
1	40	1.6	9.0
2	41	2.0	2.6
3	48	2.9	6.4
4	49	1.4	3.2
5	50	2.0	2.5
6	54	2.1	2.7
7	60	2.7	4.0
8	62	4.5	4.8
9	63	2.3	5.9
10	64	3.2	3.8

said of the creatinine. In case 1 in this group the values for urea and creatinine are normal, while there is retention of sulphates. With a difference of 1 mg in each 100 cc of blood, there is practically twice as much creatinine in each 100 cc of blood in case 8 as in case 9.

In all the determinations, the values for inorganic serum sulphates are relatively higher than for the creatinine. There are wide variations but the significant thing is that when there is a definite retention of either urea or creatinine, or an increase in sulphates, there is usually retention or increase of the other two. There are exceptions to this, an example of which is case 1, table 5. It may be that variations in renal lesions account for some of the variations observed in the relative degree of retention of urea, creatinine and sulphates. This does not explain the possibilities for the wide variations in values for inorganic serum sulphates. Attempts have been made to ascertain some of the conditions which influence the level of inorganic serum sulphates. Following Denis' suggestion that diuresis may influence the level of serum sulphates the following experiments were carried out.

In five cases of edema of renal origin in which merbaphen was given intravenously in doses of 2 cc, inorganic serum sulphates were determined just before and six hours after the administration of the drug, with the results shown in table 6. It is seen that in every case there is a small but a definite decrease in the sulphates after diuresis.

In another set of experiments designed to test the influence of the intake and output of fluid on inorganic serum sulphates, patients with suspected renal disease were given the water and concentration tests of Volhard and Fahr, in the order named. On the morning of the day for

TABLE 6—*Comparison of Inorganic Serum Sulphates Before and After Intravenous Administration of 2 cc of Merbaphen*

Case	Sulphates Before Merbaphen, Mg Sulphate in Each 100 Cc of Serum	Sulphate Six Hours After Merbaphen Mg Sulphate in Each 100 Cc of Serum	Amount of Urine Voided During the Six Hour Period After Merbaphen, Cc
1	2.5	2.3	1,800
2	3.0	2.9	1,500
3	2.3	2.0	1,200
4	3.2	2.5	1,750
5	2.3	1.3	1,000

\* Patients received a carefully weighed diet, with daily fluids less than 1,000 cc.

TABLE 7—*Comparison of Inorganic Serum Sulphates Before and After the So-Called Water and Concentration Tests of Volhard and Fahr*

Case	Before 1,500 Cc of Water by Mouth	Four Hours After 1,500 Cc of Water by Mouth	Thirty Hours Without Water Except the 200 Cc in the Diet
1	1.3	0.7	0.9
2	1.6	1.6	1.5
3	1.5	1.4	2.1
4	2.2	2.3	2.1
5	1.9	2.2	2.1
6	9.8	8.5	10.9
7	6.8	7.1	7.0
8	1.5	1.4	1.7
9	1.2	1.1	1.5
10	1.8	1.2	2.0

the water test, before the water was given, blood was taken for the determination of sulphates. Breakfast was omitted, and 1,500 cc of water was given at 8 a. m. At noon, after the diuresis caused by the intake of water, another sample of blood was taken for determination of sulphates. The changes after diuresis caused by intake of water were not significant. A day intervened between the water and the concentration tests, during which the patient was allowed a liberal intake of fluid and a low protein diet. After the patient had been receiving the "concentration diet" for about thirty hours, during which time the water in the foods of this diet was all the patient had, blood was taken for determination of sulphates. The results are shown in table 7. The

evidence of renal insufficiency in cases 6 and 7 are tabulated in table 8, in this group, in cases 6 and 7 there was definite renal insufficiency. It is interesting to note that only in these two cases was there a definite increase in sulphates while the patients were undergoing the concentration test. This is pointed out here because it may be significant and, too, this observation is in accord with some data I have on inorganic serum sulphates in Addison's disease.

Apropos of the effect of diuresis on serum sulphates, two patients with diabetes insipidus were studied. Both of the patients were men.

TABLE 8—Evidence for a Diagnosis of Renal Insufficiency in Cases 6 and 7 in Table 7

Case	Urine Analysis		Phenolsulphonphthalein		Blood Urea, Mg in Each 100 Cc	Blood Creatinine, Mg in Each 100 Cc	Lowest Specific Gravity on Water Test	Highest Specific Gravity on Concentration Test	Blood Pressure, Mm of Hg	
			Hemo-globin (Dare) per Cent	Recoveried at the End of Two Hours					Sys-tolic	Dias-tolic
6	Hyaline casts	++	60	15%	85	3.3	1.004	1.014	180	100
	Granular casts	++								
	Red blood cells	++								
	Pus	+++								
7	Hyaline casts	+++	40	20%	74	2.4	1.005	1.015	130	85
	Granular casts	++								
	Red blood cells	+++								
	Pus	+								

TABLE 9—Inorganic Serum Sulphates in Chronic Nephrosis

Case	Sulphates, Mg in Each 100 Cc of Serum
1	1.8
2	3.0
3	1.4
4	1.5
5	2.0

and were voiding more than 4,000 cc of urine daily. Determinations on one of them showed 0.5 and on the other, 0.4 mg of sulphate in each 100 cc of serum. The quantity of sulphates in the serum of these patients was of a low normal value. Diuresis, of course, influences the level of serum sulphates, but in these two cases prolonged diuresis had failed to do more than lower the sulphates to low normal values.

Five cases of nephrosis in which blood urea and creatinine were normal were studied, with the results shown in table 9. The values for inorganic serum sulphates in these five cases of nephrosis are, on an average, higher than the average normal values given in table 1. But the values in table 9 are not higher than values obtained on patients hospitalized for causes other than renal disease, as shown in table 2.

## SUMMARY

In cases of renal insufficiency, when the blood urea is above 100 mg in each 100 cc, values for inorganic serum sulphate are high

With blood urea values between 70 to 100 mg in each 100 cc, serum sulphate concentration usually is increased. However, this increase in serum sulphates apparently has no direct correlation with blood urea and creatinine concentrations

Some evidence is offered that diuresis lowers the inorganic serum sulphates

Determination of inorganic serum sulphates in the five cases of chronic nephrosis studied were approximately normal. This would indicate that there may not be any retention of inorganic sulphate in nephrosis

Attention is called to the fact that patients who do not show evidence of renal disease may have higher inorganic serum values for sulphate than those observed in normal active persons



# A CHEMICAL STUDY OF URINE AS EFFECTED BY COMBINATIONS OF AMMONIUM CHLORIDE AND METHENAMINE\*

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AND  
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Since the classic paper of Hanzlik and Collins,<sup>1</sup> the use of methenamine has been greatly restricted, and it finds its chief application as a urinary antiseptic in acid urines. In this work acid sodium phosphate is suggested as an acidifying agent, and this suggestion is now found in most textbooks. Since that time ammonium chloride has been recommended for the same purpose, and Helmholz<sup>2</sup> reported favorably on the combined use of methenamine and ammonium chloride in pyelitis in children.

Trendelenburg<sup>3</sup> reported the dissociation curve of methenamine at increasing degrees of acidity. At a  $p_H$  of 5.2 and at a temperature of 38 C, about 8 per cent of the drug is hydrolyzed in six hours. In two hours considerably less than this, approximately 3.4 per cent will be converted into formaldehyde. At a  $p_H$  of 6.3, about 1 per cent is hydrolyzed in two hours. In six hours he found only 1.5 per cent.

In the urine, one may hope to approach a  $p_H$  of 5.2 ( $\pm 0.2$ ). Assuming that 8 per cent were hydrolyzed, a dose of 100 grains (6 Gm) would throw about 0.5 Gm of formaldehyde into approximately 2,000 cc of urine, making a concentration of 1/4,000. If the  $p_H$  is 6.3 per cent, the maximum calculated concentration would be about 1/20,000. In no case would these maximum values be obtained, nor would uniform concentrations of formaldehyde result in tests on different patients nor in tests made during different periods of the day on the same patient. Falk and Sugiura<sup>4</sup> showed that the concentration of methenamine recovered in the urine varied from 45 to 92 per cent when the drug is taken in doses of 15 grains (0.97 Gm). It is therefore evident that the difference between futile and effective urinary antiseptics

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\* Submitted for publication, Feb 23, 1929

\* From the Research Laboratories, The Upjohn Company

1 Hanzlik, P J, and Collins, R J. Hexamethylenamin. The Liberation of Formaldehyde and the Antiseptic Efficiency under Different Chemical and Biological Conditions, *Arch Int Med* **12** 578 (Nov) 1913

2 Helmholz, H F. Therapeutic Value of Hexylresorcinol in Chronic Pyelitis of Childhood, *Am J Dis Child* **32** 396 (Sept) 1926

3 Trendelenburg, Paul. *Biochem Ztschr* **95** 146, 1919

4 Falk, K G, and Sugiura, K. *J Pharmacol & Exper Therap* **8** 39, 1915

can be explained readily on the basis of known factors, furthermore, the effect of the drug is easily lost

The question of proper dosage of each of the factors is therefore important, and all results not obtained on a standard basal diet are of little help as the diet itself without a doubt frequently offsets the effectiveness of the urinary acidifier. If the diet contains milk, the high buffer action of the inorganic salts will without a doubt offset the effectiveness of acid sodium phosphate in this direction. As a matter of fact, the common use of this acidifier requires dietary directions at the same time, for Henderson and Palmer<sup>5</sup> showed that its acidifying effect was mild, and Hanzlik and Collins<sup>1</sup> gave it in purgative doses to secure a desirable liberation of formaldehyde.

#### EXPERIMENTAL CONDITIONS

To secure further information we varied the time and dosage of methenamine and ammonium chloride over a considerable range, to find out what quantities would prove sufficient on a basal diet which gave a bland neutral urine. The conditions of the experiments were as follows:

*Diet*—It was desired to select a basal diet that would allow plenty of food, be nearly normal, easily reproducible and give the urine a  $p_H$  of from 6.5 to 7 so as to make changes in acidity definitely marked. The following diet was satisfactory in these respects:

White bread, 250 Gm  
Boiled potatoes, 300 Gm  
Canned tomatoes, 150 Gm  
Canned peaches, 250 Gm  
Bananas, 150 Gm  
Canned asparagus, 100 Gm  
Butter, 90 Gm  
Milk, 1 pint  
Cream,  $\frac{1}{2}$  pint  
Water as desired

*Subjects*—The subjects for the experiment were normal young men employed around the plant by day at light labor. They were restricted in no way except as to food and drink.

*Samples*—Samples of urine were collected in most cases at intervals of two hours from 8 a. m. until 10 p. m. The next sample was collected at 6 a. m. and together with those previously collected made up the twenty-four hour sample. The samples were all preserved under toluene. The various determinations were made as soon as the samples were voided.

<sup>5</sup> Henderson, L. J., and Palmer, W. W. *J. Biol. Chem.* **14**: 81, 1913.

*Methenamine*—Methenamine was qualitatively determined by the bromine water test. A few drops of bromine water added to the urine gave an abundant orange precipitate in the presence of methenamine.

*Titratable Acidity*—A 10 cc sample of urine was titrated in the usual manner with tenth-normal alkali and phenolphthalein. The result was expressed as cubic centimeters of tenth-normal sodium hydroxide per hundred cubic centimeters of urine.

*Hydrogen Ion Concentration*—The hydrogen ion concentration was determined electrometrically by the use of a Leeds and Northrup potentiometer and a quinhydrone electrode.

*Formaldehyde*—The amount of formaldehyde was estimated by a modification of the phloroglucin colorimetric method of Hanzlik and Collins<sup>1</sup>. Congo-red solutions were prepared and standardized against solutions of formaldehyde of known concentration. Smaller volumes were used than in the original method of Hanzlik.

*Plan of Experiment*—The basal diet was fed for two or three days until the average twenty-four hour  $p_H$  was fairly constant and approximately 6.5. Considerable experience with the diet on numerous subjects showed that the urinary  $p_H$  would be approximately 6.5 when the diet was fed until the  $p_H$  of the urine remained practically constant. When this point of equilibrium was reached (usually in from two to three days), the substances to be tried were given, dissolved in water.

## EXPERIMENTS

EXPERIMENT 1—Two subjects, W. B. and F. D., were fed the basal diet for two days, and during the next three days were fed in addition five doses daily of a mixture of ammonium chloride, 15 grains (0.97 Gm.), and methenamine,  $7\frac{1}{2}$  grains (0.49 Gm.), making 75 grains (4.87 Gm.) of ammonium chloride and  $37\frac{1}{2}$  grains (2.43 Gm.) of methenamine per day. The doses were given at 9 a. m., 11:30 a. m., 2 p. m., 4:30 and 7 p. m. Each dose was taken in approximately from 6 to 8 ounces of water. Samples of urine were collected at 8 a. m., 10, 12 noon, 2 p. m., 4, 6, 8 and 10 p. m. The amount of formaldehyde, H-ion concentration, titratable acidity, methenamine and volume were determined as soon as the samples were voided. The remainder of the samples were combined, preserved under toluene, and after the complete twenty-four hour output was obtained the H-ion concentration and acidity were determined on this composite sample. The data for this sample are listed as "twenty-four hour average" in the accompanying tables. The subjects were fed at 8 a. m., 12 noon and 5 p. m. The data are shown in table 1 and are illustrated in chart 1.

In table 1, it is shown clearly that while the urinary acidity of the subject is controlled desirably at points where hydrolysis can be expected, nevertheless, the dosage of methenamine is rather low, since the concentration of formaldehyde approximates 1:35,000. The early morning urine shows uniformly a concentration of 1:40,000, and dur-

TABLE 1—Results of Experiment 1

Time	Vol- ume	Titrat- able Acidity	pH	Remarks	Vol- ume	Titrat- able Acidity	pH	For malde- hyde	Meth- en- amine	Remarks
Subject 1 First Day					Third Day					
10 a m	165	34.0	5.72	Basal diet period	195	7.0	6.44	None	+	Five doses of methenamine, 7½ grains,
12 m	530	2.2	6.86		115	31.0	5.68	1 60,000	+	
2 p m	220	7.5	6.84	Two days	230	25.0	5.52	1 50,000	+	ammonium chloride, 15 grains at 9
4 p m	430	4.5	6.48		130	56.0	5.38	1 50,000	+	
6 p m	270	7.0	6.48	End of first day	165	48.5	5.51	1 30,000	+	11 30, 2 1 30, 7
8 p m	370	4.5	7.14		345	11.5	6.02	1 100,000	+	
10 p m	135	1.5	7.40	End of third day	140	34.0	5.96	1 60,000	+	End of third day
6 a m	400	14.5	6.42		330	40.0	5.72	1 40,000	+	
24 hour average	2,520	7.0	6.81		1,700	27.0	5.80		+	
Second Day					Fourth Day					
8 a m					115	34.0	5.80	1 60,000	+	
10 a m	70	23.0	6.22		130	25.0	5.66	1 100,000	+	
12 m	80	13.0	6.46		220	25.5	5.42	1 50,000	—	Same dose
2 p m	235	8.0	6.60		420	18.0	5.36	1 40,000	+	
4 p m	100	21.0	6.10		165	55.0	5.29	1 30,000	+	
6 p m	155	14.0	6.44		165	54.0	5.34	1 25,000	+	
8 p m	320	3.5	7.12	End of second day	205	24.5	5.41	1 40,000	+	End of fourth day
10 p m	145	3.0	7.60		145	41.5	5.52	1 50,000	+	
6 a m	470	14.0	6.72		355	41.5	5.65	1 40,000	+	
24 hour average	1,575	8.5	6.91		1,920	32.0	5.51			
Fifth Day										
8 a m					100	40.0	5.76	1 80,000	+	
10 a m					105	36.5	5.56	1 100,000	+	
12 m					220	22.5	5.48	1 50,000	—	Same dose
2 p m					345	19.0	5.48	1 50,000	+	
4 p m					270	29.0	5.50	1 45,000	+	
6 p m					175	48.5	5.31	1 35,000	+	
8 p m					330	22.0	5.44	1 40,000	+	End of fifth day
10 p m					185	34.0	5.48	1 35,000	+	
6 a m					420	34.5	5.68	1 40,000	+	
24 hour average					2,150	29.0	5.66		+	
Subject 2 First Day					Third Day					
10 a m	340	12.5	6.58	Basal diet	135	16.0	6.08		+	Five doses of methenamine
12 m	135	14.5	6.68		90	46.5	5.41	1 50,000	+	
2 p m	220	8.0	6.88		410	18.0	5.46	1 50,000	+	7½ grains ammonium chloride, 15 grains at 9
4 p m	155	9.0	7.14		165	51.5	5.30	1 30,000	+	
6 p m	180	12.0	7.12	End of first day	80	84.5	5.42	1 25,000	+	11 30, 2 1 30 7
8 p m	520	3.5	7.20		115	58.5	5.36	1 50,000	+	
10 p m	90	9.0	7.44	End of third day	90	65.5	5.64	1 35,000	+	End of third day
6 a m	520	23.0	6.26		650	29.5	5.72	1 40,000	+	
24 hour average	2,150	9.5	6.78		1,735	32.0	5.66			
Second Day					Fourth Day					
8 a m					70	33.0	5.36	1 90,000	+	Same dose
10 a m	115	6.5	7.00		120	28.5	5.24	1 100,000	—	
12 m	80	17.5	6.54		110	50.5	5.28	1 50,000	—	
2 p m	100	29.0	6.44		280	37.5	5.12	1 30,000	—	
4 p m	120	16.0	6.84		205	51.0	5.24	1 25,000	+	
6 p m	170	14.0	6.84		110	88.0	5.36	1 30,000	+	
8 p m	260	7.0	6.68	End of second day	210	40.5	5.24	1 30,000	+	
10 p m	105	7.5	7.36		300	22.0	5.64	1 50,000	+	
6 a m	530	19.5	6.18		605	36.5	5.68	1 40,000	—	
24 hours average	1,480	14.5	6.66		2,010	37.5	5.50		+	
Fifth Day										
8 a m					90	31.0	5.41	1 100,000	—	Same dose
10 a m					215	18.0	5.07	1 100,000	—	
12 m					200	34.0	5.16	1 40,000	+	
2 p m					375	28.5	5.16	1 30,000	+	
4 p m					385	21.5	5.24	1 30,000	—	
6 p m					140	52.0	5.40	1 35,000	—	
8 p m					345	24.5	5.27	1 40,000	—	
10 p m					245	22.0	5.50	1 45,000	—	
6 a m					520	38.5	5.56	1 35,000	—	
24 hours average					2,715	27.5	5.48		—	

ing the early hours of the day about four hours are required to bring the urinary concentration again up toward the maximum

EXPERIMENT 2—This experiment was carried out exactly as experiment 1, except that the two subjects, WB and FD, were given a larger dose of methenamine. They received 15 grains each of ammonium chloride and methenamine at regular intervals, avoiding meals as far as possible. For two days five doses were given and on the last day seven doses. A third subject, EG, was kept on the original dosage

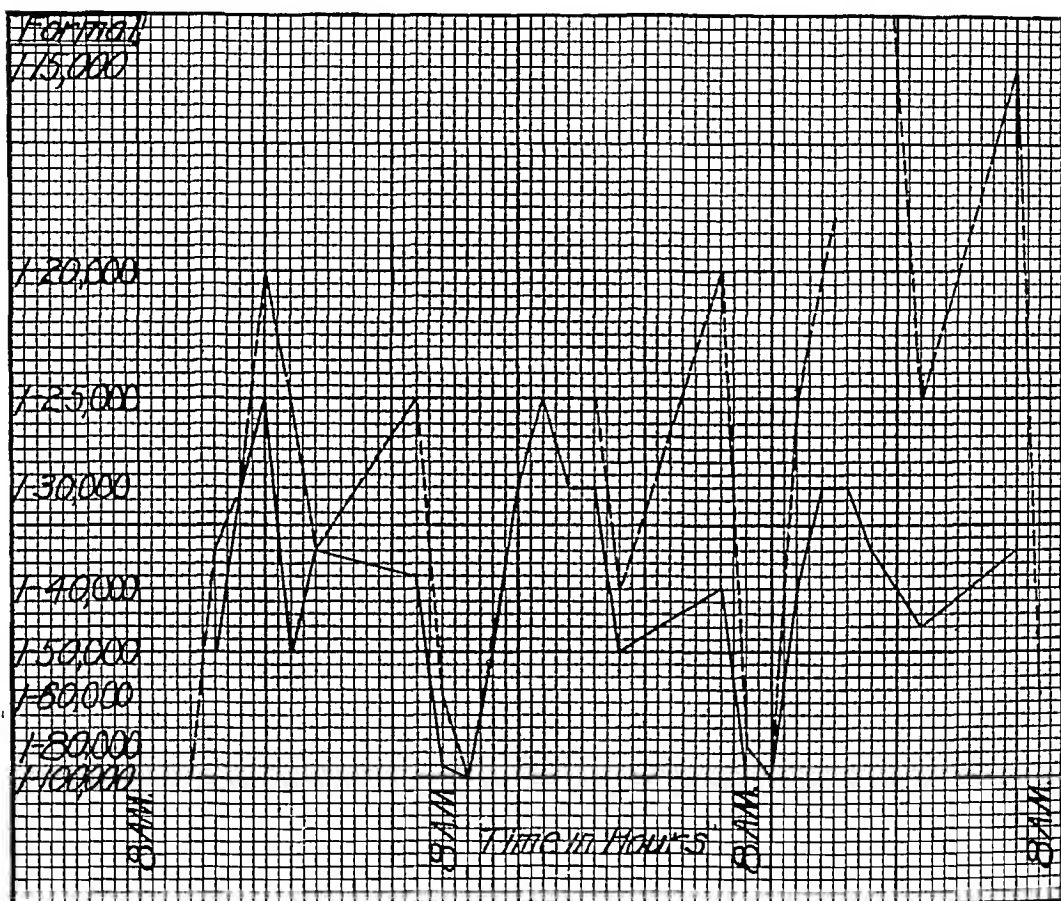


Chart 1—Difference in effectiveness of 15 over 7½ grains of methenamine with 15 grains of ammonium chloride. The broken line represents the results from 75 grains, the solid line, from 37½ grains

For the days on which 75 grains of methenamine was given, it will be observed that (although the urinary acidity is approximately the same as in experiment 1) the concentration of formaldehyde is of a somewhat higher order, approximately 1:30,000. Particularly the early morning urine showed a much higher concentration of about 1:20,000.

In general, it must be admitted that so far as the urinary concentration of formaldehyde in the day-time urine was concerned, at the same  $p_H$  there was but little increase due to the additional methenamine. We therefore extended the experiment on the third day to seven doses,

TABLE 2—Results of Experiment 2

Time	Volume	Titrat- able Acidity	pH	Remarks	Volume	Titrat- able Acidity	pH	For malde- hyde	Meth en- amine	Remarks
Subject 1				First Day	Third Day					
10 a m	95	72.5	5.60		120	22.0	6.54		+	Five doses of
12 m	170	3.5	6.51		495	6.0	6.28	+1 100,000	+	methenamine,
2 p m	370	4.5	6.27		355	17.0	5.74	1 30,000	+	15 grains,
4 p m	125	30.5	5.66		140	52.0	5.63	1 30,000	+	ammonium
6 p m	95	29.0	6.27		195	35.5	5.63	1 25,000	+	chloride, 15
8 p m	220	8.0	6.83		130	31.0	5.72	1 35,000	+	grains, at 9,
10 p m	170	4.0	7.53		110	53.5	5.74	1 50,000	+	11 30, 2, 1 30, 7
6 a m	345	21.5	6.46		330	35.0	5.81	1 25,000	+	
24 hour average	1,890	11.0	6.49		1,875	22.0	5.84		+	
				Second Day	Fourth Day					
8 a m					90	37.0	5.65	1 50,000	+	
10 a m	130	34.5	6.13		240	16.5	5.74	1 100,000	+	
12 m	420	5.0	6.50		330	17.0	5.66	1 50,000	+	
2 p m	275	9.0	6.81		440	16.0	5.65	1 35,000	+	Same dose
4 p m	100	18.0	6.62		155	52.5	5.54	1 25,000	+	
6 p m	110	24.0	6.42		340	25.5	5.55	1 30,000	+	
8 p m	240	5.0	7.22		400	17.5	5.75	1 40,000	+	
10 p m	170	3.0	7.55		345	14.5	5.92	1 50,000	+	
6 a m	470	14.0	6.68		255	54.5	5.60	1 20,000	+	
24 hour average	1,915	9.0	6.80		2,595	21.0	5.65			
				Fifth Day						
8 a m					75	39.0	5.76	1 50,000	+	Seven doses of
10 a m					155	24.0	5.54	1 60,000	+	same sub-
12 m					210	32.5	5.48	1 25,000	+	stances at
2 p m					530	15.5	5.33	1 25,000	+	8 30, 10, 11 30,
4 p m					75	63.5	5.30	1 20,000	+	1, 3, 7, 9
6 p m					120	56.5	5.31	1 10,000	+	
8 p m					300	21.0	5.88	1 35,000	+	
10 p m					170	34.5	5.76	1 25,000	+	
6 a m					145	41.5	5.56	1 25,000	+	
24 hours					1,780	25.0	5.65		+	
8 a m					70	44.0	5.51	1 40,000	+	
Subject 2				First Day	Third Day					
10 a m	170	23.5	5.77		370	5.5	6.61		+	Five doses of
12 m	75	24.0	6.01		520	6.5	6.03+	1 100,000	+	methenamine,
2 p m	110	27.5	6.44		425	20.0	5.58	1 35,000	+	15 grains,
4 p m	100	19.0	6.64		430	17.5	5.50	1 30,000	+	ammonium
6 p m	55	45.0	6.75		140	63.5	5.65	1 20,000	+	chloride, 15
8 p m	145	22.5	5.98		115	54.5	5.56	1 25,000	+	grains, at 9,
10 p m	50	35.0	6.32		330	23.0	5.69	1 35,000	+	11 30, 2, 4 30, 7
6 a m	370	28.5	6.18		505	39.0	5.77	1 25,000	+	
24 hour average	1,075	25.0	6.18		2,732	25.5	5.77			
				Second Day	Fourth Day					
8 a m					110	25.5	5.79	1 60,000	+	
10 a m	225	5.5	7.14		200	15.5	5.57	1 100,000	+	
12 m	80	11.0	7.08		495	15.5	5.64	1 45,000	+	Same dose
2 p m	175	17.0	6.80		390	23.0	5.41	1 30,000	+	
4 p m	490	6.0	6.90		495	19.5	5.44	1 25,000	+	
6 p m	75	26.5	6.74		310	32.0	5.64	1 25,000	+	
8 p m	205	9.5	6.66		330	21.0	5.46	1 25,000	+	
10 p m	445	3.0	7.43		385	18.0	5.74	1 40,000	+	
6 a m	465	14.0	6.47		430	50.5	5.72	1 20,000	+	
24 hour average	2,160	9.0	6.88		3,145	24.0	5.63		+	
				Fifth Day						
8 a m					250	14.0	5.81	1 80,000	+	Seven doses of
10 a m					390	10.0	5.48	1 100,000	+	same sub-
12 m					265	37.0	5.46	1 25,000	+	stances at
2 p m					355	31.0	5.33	1 20,000	+	8 30, 10, 11 30,
4 p m					200	61.0	5.42	1 10,000	+	1, 3, 7, 9
6 p m					95	96.5	5.51	1 10,000	+	
8 p m					80	62.5	5.58	1 15,000	+	
10 p m					105	59.0	5.65	1 25,000	+	
6 a m					385	44.0	5.70	1 15,000	+	
24 hr av					2,125	31.0	5.61		+	
8 a m					265	11.0	5.36	1 60,000	+	

TABLE 2—Results of Experiment 2—Continued

Time	Vol- ume	Titrat able Acidity	p <sub>H</sub>	Remarks	Vol- ume	Titrat- able Acidity	p <sub>H</sub>	For- malde- hyde	Meth- en- amine	Remarks
Subject 3	First Day				Third Day					
10 a m	65	53.0	6.80		245	12.0	6.80		+	Five doses of
12 m	75	25.5	6.73		160	35.0	5.94	1 60,000	+	methenamine,
2 p m	220	13.0	6.86		130	55.0	5.99	1 50,000	+	15 grains,
4 p m	365	6.0	7.00		200	40.5	6.02	1 60,000	+	ammonium
6 p m	60	49.5	6.21		380	26.5	5.79	1 50,000	+	chloride, 15
8 p m	230	10.5	6.98		540	12.0	6.13	1 100,000	+	grains at 9,
10 p m	310	4.0	7.25		125	42.0	5.87	1 45,000	+	11 30, 2, 4 30, 7
6 a m	405	23.5	6.01	End of	255	73.5	5.65	1 10,000	+	
24 hour				first day						
average	1,730	12.5	6.71		2,035	27.5	5.97		+	
	Second Day				Fourth Day					
8 a m					65	50.5	5.63	1 50,000	+	
10 a m	115	20.0	6.69		75	52.0	5.60	1 100,000	+	
12 m	80	29.5	6.68		120	68.0	5.72	1 50,000	+	Same dose
2 p m	280	13.5	6.47		140	71.0	5.49	1 30,000	+	
4 p m	85	57.0	5.94		260	42.0	5.55	1 30,000	+	
6 p m	95	39.0	6.13		210	54.5	5.46	1 20,000	+	
8 p m	145	15.0	6.64		280	28.5	5.56	1 25,000	+	
10 p m	240	6.0	7.08		195	33.0	5.51	1 30,000	+	
6 a m	155	64.5	5.68	End of	565	39.5	5.53	1 25,000	+	
24 hour				second day						
average	1,195	23.0	6.35		1,910	41.0	5.63		+	
	Fifth Day									
8 a m					105	20.5	5.70	1 70,000	+	
10 a m					320	18.0	5.63	1 70,000	+	Same dose
12 m					140	53.0	5.56	1 45,000	+	
2 p m					120	73.5	5.43	1 25,000	+	
4 p m					140	74.5	5.39	1 25,000	+	
6 p m					70	84.0	5.14	1 30,000	+	
8 p m					285	33.5	5.47	1 25,000	+	
10 p m					420	17.0	5.56	1 30,000	+	
6 a m					750	24.5	5.48	1 40,000	+	
24 hr av					2,350	28.0	5.51		+	
8 a m					70	53.5	5.41	1 100,000	+	

increasing the intake of ammonium chloride to 105 grains (6.82 Gm). This perceptibly lowered the  $p_H$ , and the combined effect was to increase the concentration of urinary formaldehyde to the order of 1 25,000 or more, the early morning urine, in the case of F D, showing a concentration of 1 15,000.

EXPERIMENT 3—This is an experiment in which the subjects started on the same dosage as in experiment 1, with five doses of methenamine and ammonium chloride, so that during the day 37½ grains of the former and 75 grains of the latter were given. This was then raised on the third day to seven doses, giving a third intake of 52½ and 105 grains (3.43 and 6.82 Gm), respectively. It can be observed at once from table 3 that at the 7½ grain level for methenamine, even at seven times a day, the urinary concentration of formaldehyde is far below that found in experiment 2 in which 15 grains of methenamine was given from five to seven times a day.

The difference in the effectiveness of 15 over 7½ grains of methenamine with 15 grains of ammonium chloride is shown in charts 1 and 2. In the first subject, F D, on five doses per day, the concentration was raised from approximately 1 45,000 to 1 30,000 on the first day. On the second day the higher dose maintained 1 30,000, while with the lower dose the urine during a large part of the time showed ineffectual concentration. With seven doses, the higher intake

TABLE 3—Results of Experiment 3

Time	Volume	Titrat-able Acidity	pH	Remarks	Volume	Titrat-able Acidity	pH	Formaldehyde	Methenamine	Remarks
Subject 1 First Day					Third Day					
10 a m	90	49.0	5.66		65	20.5	6.23		+	Five doses of
12 m	165	10.5	6.16		90	13.5	5.62	1 60,000	+	methenamine,
2 p m	540	4.5	6.74		250	27.0	5.24	1 45,000	+	7½ grains,
4 p m	115	16.0	6.78		90	63.0	5.48	1 45,000	+	ammonium
6 p m	115	23.5	6.35		105	67.5	5.43	1 40,000	+	chloride, 15
8 p m	270	7.0	6.68		100	11.5	5.44	1 50,000	+	grains, at 9,
10 p m	100	9.0	7.11		100	49.0	5.53	1 40,000	+	11 30, 2, 4 30, 7
6 a m	245	29.5	6.27		385	44.5	5.70	1 30,000	+	
24 hour average	1,640	12.5	6.52		1,185	40.5	5.69		+	
Second Day					Fourth Day					
8 a m					70	37.0	5.85	1 70,000	+	
10 a m	75	23.0	6.35		80	51.5	5.77	1 100,000	+	
12 m	85	11.5	7.20		95	59.0	5.62	1 40,000	+	
2 p m	285	5.5	7.14		200	46.5	5.36	1 35,000	+	Same dose
4 p m	225	15.0	6.86		115	70.5	5.46	1 40,000	+	
6 p m	205	8.0	7.33		75	77.5	5.43	1 45,000	+	
8 p m	320	3.5	7.40		130	46.0	5.48	1 40,000	+	
10 p m	145	3.5	7.73		120	97.5	5.61	1 50,000	+	
6 a m	385	11.5	6.88		315	51.0	5.68	1 40,000	+	
24 hour average	1,625	8.0	7.12		1,200	48.0	5.68			
Fifth Day										
8 a m					70	51.5	5.74	1 100,000	+	Seven doses of
10 a m					230	20.5	5.65	1 100,000	+	same sub
12 m					230	31.0	5.56	1 40,000	+	stances at
2 p m					370	27.0	5.27	1 30,000	+	8 30, 10, 11 30,
4 p m					185	73.5	5.20	1 25,000	+	1, 3, 7, 9
6 p m					175	38.0	5.31	1 35,000	+	
8 p m					195	26.5	5.25	1 40,000	+	
10 p m					150	44.0	5.37	1 35,000	+	
6 a m					230	59.0	5.46	1 50,000	+	
24 hr av					1,835	33.5	5.48		+	
8 a m					135	30.5	5.36	1 70,000	+	
Subject 2 First Day					Third Day					
10 a m	225	4.0	7.02		215	4.0	6.71		+	Five doses of
12 m	145	6.5	7.44		205	27.5	5.80	1 80,000	+	methenamine,
2 p m	115	15.0	7.40		225	46.0	5.48	1 40,000	+	7½ grains
4 p m	120	15.0	7.14		135	64.0	5.56	1 35,000	+	ammonium
6 p m	85	38.5	6.66		175	47.0	5.53	1 35,000	+	chloride 15
8 p m	85	25.0	6.63		305	27.0	5.46	1 40,000	+	grains, at 9
10 p m	380	5.0	7.10		350	18.5	5.85	1 60,000	+	11 30, 2, 4 30, 7
6 a m	350	27.0	6.10		580	35.5	5.82	1 40,000	+	
24 hour average	1,505	12.0	6.80	End of first day	2,190	27.5	5.77		—	
Second Day					Fourth Day					
8 a m					235	10.0	5.85	1 100,000	—	
10 a m	180	3.0	7.20		420	13.0	5.37	1 100,000	+	
12 m	120	13.5	6.64		195	36.0	5.58	1 40,000	+	Same dose
2 p m	110	20.5	6.85		125	73.0	5.51	1 35,000	—	
4 p m	125	18.5	6.86		160	67.0	5.55	1 35,000	—	
6 p m	95	33.5	6.34		150	61.5	5.49	1 30,000	+	
8 p m	50	37.0	6.26		385	24.5	5.44	1 35,000	—	
10 p m	175	4.0	7.07		300	24.5	5.79	1 45,000	+	
6 a m	440	19.0	6.00		790	22.5	6.00	1 70,000	—	
24 hour average	1,295	13.5	6.54	End of second day	2,750	26.5	5.76		—	
Fifth Day										
8 a m					180	13.0	5.75	1 100,000	—	
10 a m					105	23.5	5.31	1 100,000	—	Seven doses of
12 m					365	27.5	5.49	1 20,000	—	same sub
2 p m					230	52.0	5.42	1 25,000	—	stances at
4 p m					295	41.0	5.37	1 25,000	+	8 30, 10 11 30
6 p m					190	58.0	5.42	1 25,000	—	1, 3, 7, 9
8 p m					240	36.0	5.54	1 40,000	—	
10 p m					320	24.5	5.78	1 60,000	—	
6 a m					730	24.5	5.56	1 45,000	—	
24 hr av					2 655	29.5	5.54		—	
8 a m					520	17.0	5.64	1 45,000	—	



of methenamine showed a concentration of 1 20,000 well sustained. In all cases, the two hour period in the morning gave urine of low formaldehyde concentration.

In the case of W B, shown in chart 2, the advantage of the higher dose is not so pronounced but is evident from the curves.

Chart 3 shows the close relationship of the  $p_H$  curve to the concentration of formaldehyde in the case of E G, and explains the low

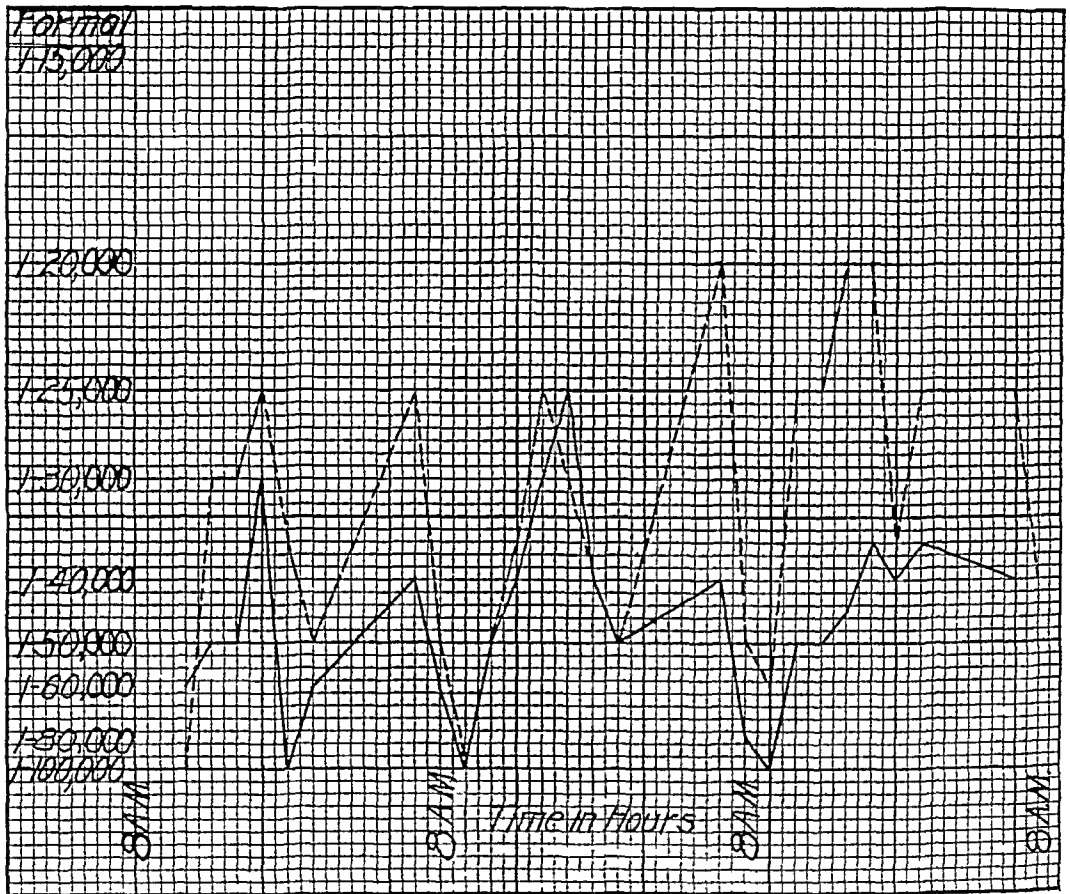


Chart 2—The advantage of the higher dose is not so pronounced, but is evident from the curves. The broken line represents the results from 75 grains, the solid line, from 37½ grains.

concentration of formaldehyde at some periods as being due, not to an insufficiency of the acidifying factor, but to lack of available methenamine.

Chart 4 shows what may be expected of ammonium chloride as a urinary acidifier in 15 grain doses. This curve is not scaled to hydrogen ion concentration but to the  $p_H$  scale which dwarfs the increased acidity as represented by the curve.



Chart 3—Close relationship of the  $p_H$  curve to the concentration of formaldehyde in the case of E G, experiment 2. The chart shows the low concentration of formaldehyde as due to the lack of methenamine. The broken line represents the formaldehyde, the solid line, the  $p_H$ . Each small square represents one hour.

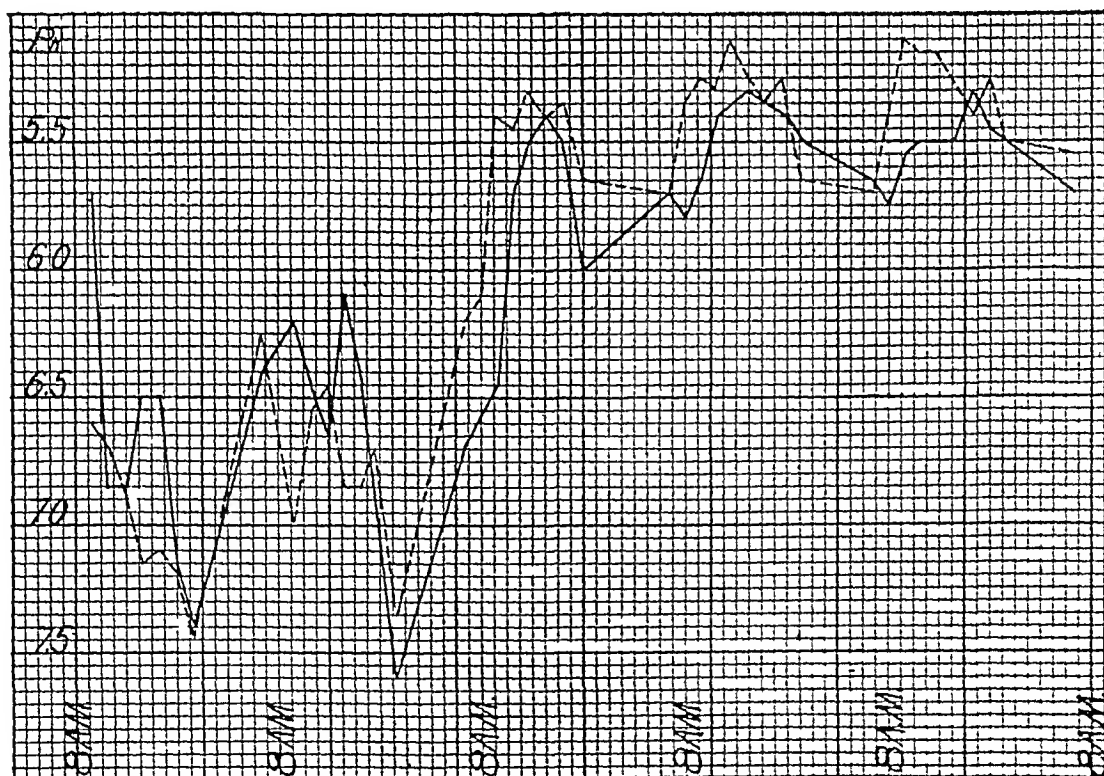


Chart 4—The effect of ammonium chloride as a urinary acidifier. The broken line represents the results for F D, the solid line for W B. Each small space represents one and a half hours.

## SUMMARY

Ammonium chloride, even against the high buffering effect of nearly neutral urine, produces a rapid acidifying effect, which at a level of 15 grains five times a day showed a  $p_H$  of about 5.5

Methenamine at a level of  $7\frac{1}{2}$  grains five times a day gave a concentration somewhat but not proportionately lower than that found at the dosage of 15 grains. The acidity is of prime importance.

In this work the dosage of methenamine varied from  $37\frac{1}{2}$  to 105 grains a day. The higher doses gave the higher concentration of formaldehyde, other factors being equal. Ammonium chloride did not yield the maximum acidifying effect until the second day.

Following the last dose in the evening, the concentration of formaldehyde fell somewhat but usually became higher during the night, owing to the length of time the urine remained in the bladder. The sample taken at 6 a. m. usually had a high formaldehyde concentration since most of the methenamine had been excreted during the night.

There is a marked drop in the formaldehyde concentration in the forenoon, but it rises rapidly as the excretion of methenamine is increased following the medication.

# THE RELATION OF WITHDRAWAL OF CEREBROSPINAL FLUID TO THE BODY TEMPERATURE CONSIDERATION OF A THERMOREGULATORY CENTER

A STUDY OF TWO HUNDRED AND FIFTY CASES \*

ALFRED GORDON, M D

PHILADELPHIA

During the course of routine examinations of the spinal fluid in neuropsychiatric patients, the following peculiarity was observed, at first accidentally. Shortly after lumbar punctures, a few patients complained of general discomfort. This circumstance led the nurses in attendance to take the temperatures of these patients. They found a slight elevation. Interested by this incidental observation, I decided to pursue this investigation further and thus commenced to gather observations on a large scale. The observations on 250 cases presented here suggest certain ideas concerning the pathogenesis of fever and the possible localization of a thermoregulatory center. The observations in adults differ somewhat from those in children. The adult group consisted of twenty-five patients with hemiplegia, five with increased intracranial pressure, seventeen with idiopathic epilepsy, ten with meningitis, forty with psychoneuroses, twelve with manic-depressive psychosis, ten with transverse myelitis, two with multiple sclerosis, fifteen with paresis, twenty with tabes, forty with severe headache of syphilitic origin and four with dementia praecox. The fifty children included ten with meningitis, fifteen mentally defective, twenty with epilepsy and five with Little's disease.

The temperature of each patient was taken immediately before, and five minutes, half an hour, one hour and three hours after the puncture of the spinal canal or of the lateral ventricles in the brain. In the adult series, the rise commenced in the majority of cases five minutes, and in some cases only thirty minutes, later. It continued to ascend until the third hour, then it gradually descended to reach the degree at which it stood before the punctures (chart 1). The highest rise was 2 F and the lowest 0.5. The greater the amount of spinal fluid withdrawn, the higher the temperature went up and the sooner the rise commenced. It was exceedingly interesting to observe that whenever spinal fluid could not be obtained on one and even on several attempts—which not infrequently happens and which usually means no penetration of the needle into the dural sac—in every such case, no change in the

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bodily temperature could be noticed. In five cases with the diagnosis of serous meningitis (judged by the typical clinical symptoms and absence of specific micro-organisms) there was a slight fever before the lumbar puncture, but the withdrawal of spinal fluid was followed by a greater rise (from 1 to 2.5 degrees) than in the afebrile cases (charts 2 and 3). The following interesting observation deserves special men-

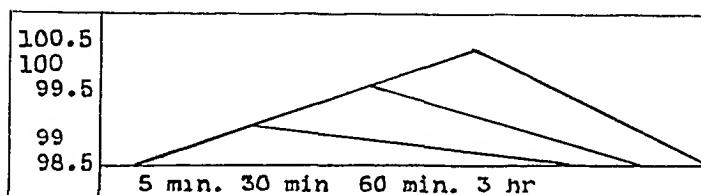


Fig 1—The rise in bodily temperature following lumbar puncture

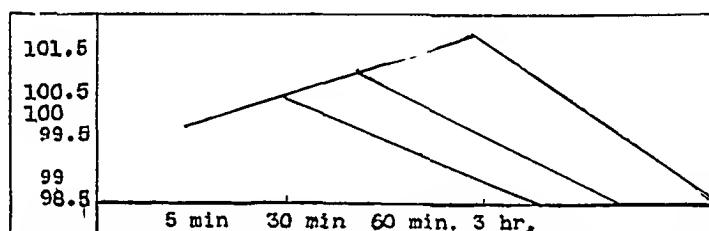


Fig 2—The rise in bodily temperature following lumbar puncture in serous meningitis

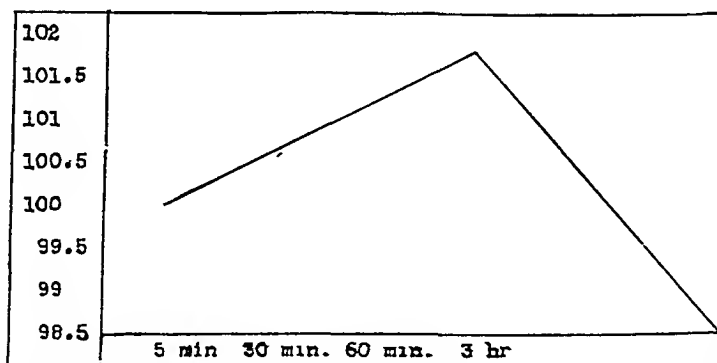


Fig 3—The rise in bodily temperature following lumbar puncture in febrile cases

tion since it apparently has a certain bearing on the pathogenesis of fever, which will be discussed later. In cases of evident meningeal irritation and especially in cases of seropurulent spinal fluid in which a definite or specific micro-organism cannot be determined, I am in the habit of injecting physiologic solution of sodium chloride following the withdrawal of spinal fluid. In the majority of such cases, I have not observed a rise but an immediate fall of the temperature after the evacuation of some of the spinal fluid, but a rapid subsequent ascension

of the temperature occurs after this solution has replaced the sero-purulent fluid (chart 4) Moreover, this rise is greater (2 degrees) than in the cases in which lumbar puncture is employed alone

In several cases of puncture of the lateral ventricles, either for ventriculography or for the alleviation of epileptic convulsions,<sup>1</sup> the removal even of a small quantity of cerebrospinal fluid, such as 5 or 10 cc, was followed by a rise of temperature and this, curiously enough, much sooner than in the case in which lumbar puncture was made,

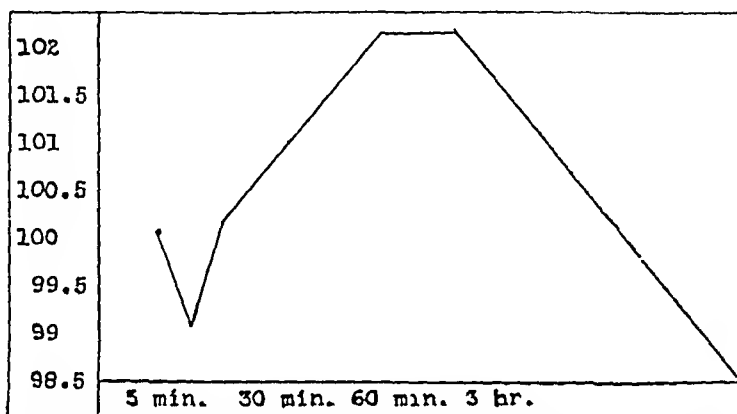


Fig 4—The rise in bodily temperature following lumbar puncture and injection of physiologic solution of sodium chloride in febrile cases

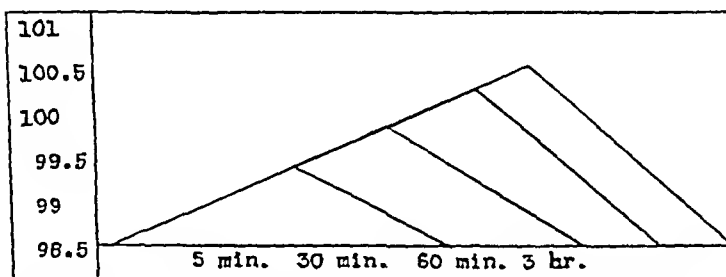


Fig 5—The rise in bodily temperature following ventricular puncture

namely, in two or three minutes (chart 5) As in the cases in which lumbar puncture was done, the larger the quantity of fluid withdrawn, the higher was the elevation of temperature When the removal of the fluid was followed by an injection of air for ventriculography or of physiologic solution of sodium chloride, as in some meningeal conditions, the rise of the temperature was more marked than in the cases without the secondary introduction of air or fluid into the ventricles (chart 6) It must be mentioned also that the duration of the elevated

<sup>1</sup> Gordon, Alfred Hydrocephalus with Cessation of Persistent Convulsions after Puncture of the Lateral Ventricles J A M A 88 1234 (April 16) 1927

temperature is greater in the cases of ventricular than in the cases of lumbar puncture, being as long as three or four or even five hours

The children presented, in general, the same picture as the adults with the exception, however, that under identical circumstances and in identical pathologic conditions they invariably showed a rise of temperature decidedly higher than did the adults. When the latter showed a rise of 0.5 degree, the children showed a rise of 1 degree, when the adults presented a rise of 1 degree, the children presented a rise of 1.5 degrees.

In each of the two groups there were some differences in the intensity and rapidity of the reaction to the withdrawal of cerebrospinal fluid. For example, in the epileptic and meningeal patients there was

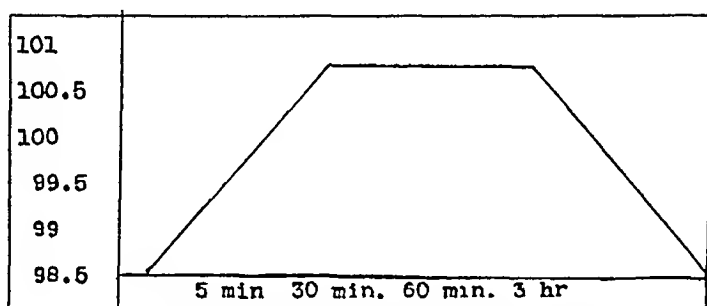


Fig 6—The rise in bodily temperature following ventricular puncture and injection of air

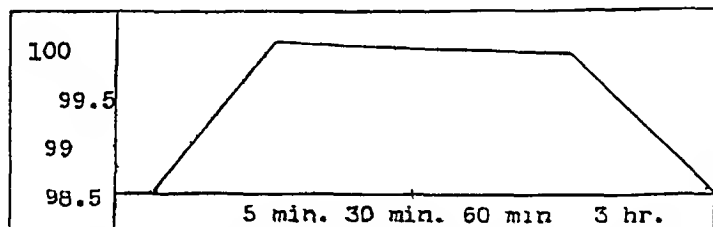


Fig 7—The rise in bodily temperature following ventricular or lumbar puncture in syphilitic headache

a quicker and greater response to punctures than in the patients who were hemiplegic. Among those with psychoses, the rise of temperature was more marked in the maniacal phases than in the depressive phases, and in the patients with manic-depressive insanity, in general, the rise was greater than in the patients with psychoneuroses. The duration of the higher temperature presented analogous differences. Patients with syphilitic headache presented an earlier, more prolonged and more marked reaction to punctures than those with tabes or those with paresis (chart 7). As to the latter two groups, the paretic patients were more conspicuous in their reaction than the tabetic ones. A more detailed account of some of these differences is presented in the charts.

## COMMENT

In summing up these facts, special attention is invited to the following considerations, which in my opinion possess a special meaning. What is the reason that a dry puncture is not followed by an elevation of temperature? What is the reason that in cases of meningitis the pre-existing febrile state becomes accentuated after a lumbar puncture? What is the reason that in cases of seropurulent cerebrospinal fluid the removal of some of it is followed by hypothermia, but as soon as a physiologic solution of sodium chloride is injected into the dural sac, the temperature rises? Although these phenomena cannot all be explained to full satisfaction, one fact nevertheless stands out and that is, a change in the stability or in the equilibrium of the cerebrospinal fluid, brought about by either ventricular or lumbar puncture and resulting in diminution of the quantity of the cerebrospinal fluid, produces a change in the bodily temperature. If this is so, the next question is "By what mechanism?" Schoenfeld<sup>2</sup> showed that the removal even of a small quantity of spinal fluid is followed by an increase in its cells and albumin contents. On this basis, one may argue that the mechanical irritation of the meninges produced by the puncture of the dural sac results in chemical and physical changes of the fluid and consequently in hyperthermia. On the other hand, one should also take into account the meningeal irritation per se produced at the time of the puncture and consider it, also, as one of the causative elements in the rise of temperature. Indeed, the observations of Thurzo and Nagy<sup>3</sup> indicate this possibility.

So far my discussion of the cause of the fever leads to consideration of two factors, namely, mechanical stimulation and meningeal irritation.

Auerbach<sup>4</sup> calls attention to the fact that an abundant loss of cerebrospinal fluid during an operation on the brain and spinal cord is frequently associated with a rise of bodily temperature. This observation as well as those of Jakobi and Roemer,<sup>5</sup> of Trendelenburg<sup>6</sup> and of Jánossy and Horvath,<sup>7</sup> suggests a new possibility, namely, that pituitary secretions, which have been found in cerebrospinal fluid, cause the increase of bodily temperature during physical disturbances of this fluid. Whether this assumption is correct or not, it is impossible at present to ascertain.

2 Schoenfeld *Deutsche Ztschr f Nervenhe*, 1919, p 64

3 Thurzo and Nagy *Deutsche Ztschr f Nervenhe*, 1923, p 374

4 Auerbach *Ztschr f d ges Neurol u Psychiat* 24 229, 1922

5 Jakobi and Roemer *Arch f exper Path u Pharmakol* 1912, p 149

6 Trendelenburg *Klin Wchnschr* 3 777, 1924

7 Janossy and Horvath *Zentralbl f d ges Neurol u Psychiat*, 1926,



The outstanding feature in all observations recorded is that when the physical relationship of the cerebrospinal fluid is disturbed in one way or another, the bodily temperature is equally disturbed. At this juncture, I may mention also the following occurrence. In one case of progressive muscular atrophy of syphilitic origin and in one case of hydrocephalus, the physicians in charge drained the spinal canal to the maximum. In each case, the body temperature rapidly became low (97 F and 96 F, respectively).

In the presence of such facts, as well as of those mentioned previously, one is firmly led to the conception that not only is there a relationship of the cerebrospinal fluid to changes in the temperature but this fluid is actually in some relationship to a thermoregulatory center. That the central nervous system, generally speaking, has a direct influence on the bodily temperature is well recognized. Experimental physiology has demonstrated the existence of a "thermic center." From among the vast number of observations in this field, suffice it to recall the experiments of Citron and Leschke,<sup>8</sup> who showed conclusively on dogs that the midbrain contains a thermic center. They infected the animals, the temperatures naturally rose, and then they sectioned the midbrain. No fever was thereafter in evidence. Isenschmidt, Krehl and Schnitzler<sup>9</sup> concluded from their own observations that the midbrain and, precisely, the tuber cinereum, play an important rôle in thermoregulation. The adjacent area, especially the floor, of the third ventricle is the most probable center of the regulation of bodily temperature. A further step was made in the more accurate localization of such a center, when Jacobi and Roemer<sup>5</sup> announced that not only a direct irritation of the walls of the ventricle, but also a transmission of a contiguous disturbing influence to them is apt to influence the bodily temperature. If one considers that there is a close relationship between the cerebrospinal fluid at any level within the brain, on the surface of the brain or in the spinal canal with the third ventricle (namely, by means of an anatomic communication of the lateral ventricles with the third through the foramen of Monro, of the fourth with the third through the aqueduct of Sylvius, of the fourth ventricle with the cisterna magna through the foramina of Magendie and Luschka and finally, of the cisterna with the spinal canal without an intermediary passage-way), if one also considers the fact that the cisterna magna is the area into which the fluid flows from every direction of the brain and which is therefore in a certain relationship to smaller collections of fluid at the base of the brain and also to that in the subarachnoid spaces on the surface of the brain, if, finally, one

8 Citron and Leschke. *Verhandl. d. Kongr. inn. Med.* **30** 65, 1913.

9 Isenschmidt, Krehl, and Schnitzler. *Arch. f. exper. Path. u. Pharmacol.*, 1912, p. 109, 1914, p. 202.

recognizes the close connection of fluid contents between the ventricular systems, the surface of the brain and the spinal canal, one can readily conceive that a physical disturbance of the fluid in the cerebrospinal system at one of its levels is bound to produce a more or less intense mechanical effect on the same fluid at other levels. If one also recalls the afore mentioned experiments of Citron and Leschke on the mid-brain, as well as of others on the area surrounding the third ventricle, one can readily understand the hyperthermia provoked by the lumbar or the ventricular puncture.

The walls of the ventricles are the only places in the central nervous system where the cerebrospinal fluid is in intimate contact with the parenchyma of nervous tissue, they are therefore physiologic centers. It stands to reason that any physical disarrangement taking place in the cerebrospinal fluid will cause a corresponding irritation of the ventricular walls and therefore of the thermic center. Removal of some fluid may produce a change in the shape or in the general configuration of the ventricle or a collapse of its walls, or else it may be the point of departure for reformation of the fluid within the emptied ventricle, which, as is well known, is a rapidly developing phenomenon when the ventricles are in a pathologic state.

Aueibach,<sup>1</sup> as stated, among many others, observed a rise of temperature during operative procedures on the cranium or on the spinal cord, which, of course, are usually accompanied by a considerable loss of cerebrospinal fluid, the hyperthermia subsided when the fluid had again reached its normal level.

It was mentioned that in two cases an erroneous maximal removal of the spinal fluid was followed by a lowering of the bodily temperature. A low temperature has been observed in intracerebral hypertension, in hydrocephalus and in traumatic injuries of the cervical cord. In all such cases, an undue pressure is undoubtedly transmitted to the fourth ventricle and to the cervical cord. This pressure, physiologically speaking, means interruption of the central and peripheral pathways the function of which is to regulate the bodily heat. That such pathways exist has been demonstrated repeatedly. Suffice it to mention the investigation of Freund and Grafe<sup>10</sup> among many others.

Whether or not one considers the rise or the fall of the bodily temperature in the course of manipulations of the cerebrospinal fluid irrespective of different circumstances under which individual variations are observed, the fact remains that a mechanical withdrawal of a certain amount of fluid has an influence on the bodily temperature. In other words at that time the thermoregulatory centers are disturbed. Since the cerebrospinal fluid takes its origin in the choroid plexuses

10 Freund and Grafe Arch f exper Path u Pharmacol 1912, p 135

or in the ependyma or in both, it is the interior of the ventricles or more precisely the ventricular walls that are of special importance in the regulation of the bodily temperature. Dilatation, narrowing or some other alteration in the configuration of the ventricles, which can all be brought on by physical manipulations of the cerebrospinal fluid, such as punctures of the ventricles or of the spinal canal, produces a mechanical irritation of the blood vessels and nerve-endings in ventricular walls and consequently a change in the bodily temperature. All experimental investigations indicate the third ventricle as playing the most important rôle in thermic regulation. There are several problems in this direction which require greater elaboration, such as the reformation of the fluid, the change in the chemical contents in the cerebrospinal fluid during physical manipulations of it, the question of a localized meningitis during punctures and finally the individual variations in the rise or the fall of temperature. Further research is indicated for the solution of these problems. The object of the present work, however, has been merely to call attention to the fact that in alterations of bodily temperature of so-called cerebral origin, disturbances in the physical relationship of the cerebrospinal fluid plays an important, if not paramount, rôle. While the subject under discussion pertains to the domain of pathologic physiology, nevertheless the practical side of it, namely, the diagnostic and prognostic value, cannot be ignored.

#### SUMMARY

Two hundred and fifty patients presenting a great variety of nervous and mental disorders were submitted to lumbar and ventricular punctures. There were a group of adults and a group of children. The bodily temperature of each patient was taken before and several times within three hours after the puncture. Elevation of temperature commenced a few minutes after every such manipulation. In some cases, physiologic solution of sodium chloride was injected in lieu of the withdrawn cerebrospinal fluid. When the punctures were dry (no fluid obtained), the temperature remained unaltered. These observations, including those concerning the variation in the degree of the elevated temperature, indicate that a change in the stability or in the equilibrium of the cerebrospinal fluid brought about by either ventricular or lumbar puncture produces a change in the bodily temperature.

#### CONCLUSIONS

The present study as well as the casual observations made by some other investigators, especially by those who, for one reason or another, had to manipulate the cerebral ventricles or the spinal canal, leads to the following conclusions:

1 There is a relationship between the cerebrospinal fluid and the changes in the bodily temperature

2 The fluid is actually in some relationship to a thermoregulatory center

3 Ventricular or spinal withdrawal of fluid produces an alteration in the configuration of the ventricles and consequently an irritation of the nerve-endings in the ventricular walls

4 The third ventricle plays the most conspicuous part in thermic regulation

# THROMBO-ANGIONECROTIC CHANGES OF THE KIDNEYS IN CHRONIC NEPHRITIS \*

BERNARD STERNBERG, M D

BROOKLYN

Classification of the anatomic changes in what appears clinically to be chronic nephritis is made difficult by the variety and peculiarity of the anatomic lesions found in the kidneys. From a purely morphologic point of view, the renal changes can be divided into two main groups (1) inflammatory changes involving primarily the glomeruli or the tubular parenchyma or both, and (2) changes involving primarily the vascular apparatus, with other changes occurring apparently secondarily. While the former condition, the nephritis sensu strictu, is easy to understand, the greatest difficulties are met with in the interpretation of the vascular renal disease.

According to the latest anatomic work in this line, vascular changes of the kidneys are to be classified, according to the size of the arteries involved, into arteriosclerotic and arteriolosclerotic changes. In the first, large discrete foci of atrophy are found with no impairment of renal function. In the arteriolosclerotic type, the individual foci of atrophy and concomitant sclerosis are smaller but more numerous, and are therefore often coalescent. Their steady advance leads finally to the impairment of renal function.

In a certain group of cases, however, the anatomic observations, as well as the clinical picture, deviate substantially from those of ordinary arteriolosclerotic nephrosclerosis. These cases have been spoken of as "malignant nephrosclerosis" (Fahr<sup>1</sup>), "combination form" (Volhard, Fahr) and "nephrocirrhosis arteriolosclerotica progressa" (Aschoff,<sup>2</sup> Loehlein<sup>3</sup>).

Several cases studied during the last few years in the laboratory of the United Israel Zion Hospital seem to shed some light on this

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\* From the Department of Laboratories, United Israel Zion Hospital

1 Fahr, Thomas, in Henke, F, and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol 6, no 1, p 405

2 Aschoff. Ueber den Begriff der "Nephrosen und Sklerosen," Deutsche med Wchnschr **43** 43, 1917

3 Loehlein, M. Ueber die entzündlichen Veränderungen der Glomeruli der menschlichen Niere und ihre Bedeutung für die Nephritis, Leipzig, S Hirzel, 1906, Zur Nephrocirrhosis Arteriolosclerotica, Med Klin **12** 136, 1916

peculiar condition Clinically, as well as morphologically, they are so similar that it is sufficient to report only one in detail

#### REPORT OF CASE

*History*—A B, a girl, aged 18, was admitted to the hospital on March 1, 1928, complaining of headache, vomiting and weakness She had had rheumatism, and tonsillectomy was performed at the age of 7 She had suffered from nocturia and polyuria These symptoms, which had been present for some months, became aggravated just prior to her admission to the hospital, and her vision became blurred

*Examination*—On physical examination, she appeared thin and apathetic The teeth were in bad condition and the throat was injected Both retinas were edematous, and both disks were markedly choked There was a blowing murmur at the apex of the heart The apex was just outside the nipple line The aortic second sound was greater than the pulmonic second sound There were no other positive observations

Her temperature on admission was 99.5 F, it rose to 101.5 on March 3, rising gradually, and reached 105 before death The pulse rate was 130 and the respiration rate was from 25 to 30 Blood pressure, systolic, was 220, diastolic, 130

The urine showed albumin, 3 plus The blood count showed hemoglobin, 65 per cent, red blood cells, 3,150,000, white blood cells, 14,800, with polymorphonuclear leukocytes 91 per cent and lymphocytes 9 per cent The blood chemistry was urea nitrogen, from 88 to 110 mg, dextrose, from 100 to 140 mg, and creatinine, from 8 to 8.8 mg The blood culture was negative

The symptoms became progressively worse She became unconscious, and died on March 7, 1928

*Necropsy*—At necropsy, a few drops of fluid were found in the pericardial sac The pericardium was dull, and the epicardium on top of the auricles, particularly on the right side, was covered with fine grayish-red fibrinous membranes, which could readily be scraped off The heart was the size of a huge man's fist Its enlargement was eccentric, as the right side of the heart was a mere appendix to the left side The musculature was pale reddish brown with areas of grayish yellow These were most conspicuous underneath the epicardium, where they formed an irregular zone of foci of various sizes and shapes The valves were thin and smooth The aorta was of normal caliber Its intima was smooth The wall of the coronary arteries was slightly thickened and seemed to be somewhat more rigid

The kidneys were rather small Their capsules stripped off with difficulty, owing to discrete adhesions, which were particularly present about the poles The greater part of the surface of the kidneys was smooth, except around the poles, where it was irregular owing to depressions and nodular projections On section the color of the kidneys was reddish gray

In the cortex, several dark red foci were found, some of which were wedge-shaped with their bases turned toward the capsule The parenchyma of the cortex, particularly between the medullary pyramids, was mottled with yellow

Both renal pelves were distended, and various calices, particularly those corresponding to the poles, were dilated In these areas, the kidney substance was thin and did not reveal its normal structure

The arteries leading to these impaired areas showed a rigid wall and patent lumen, while the rest of the renal arteries were thin and collapsed readily

The other organs did not show any unusual features on gross examination

*Diagnosis*—The diagnosis was subacute hemorrhagic glomerulonephritis, scattered arteriosclerotic atrophy of the kidneys, hypertrophy of the left side of the heart, passive congestion of the liver, lipoidosis of the suprarenal cortex, acute pericarditis, edema of the lungs

*Microscopic Observations*—On low power examination, the kidney presented several areas of necrosis. Most of these areas were pyramidal, with their bases on the capsule of the kidney, and their apexes reaching into the medulla. In some of these areas, little of the original structure was left. In others, it was merely the tubular epithelium and particularly the nuclei which showed disintegration. The lumina of the tubules were filled with a homogeneous mass. A similar exudate could also be seen within the capsules of the glomeruli. The stroma of these areas showed infiltration by leukocytes.

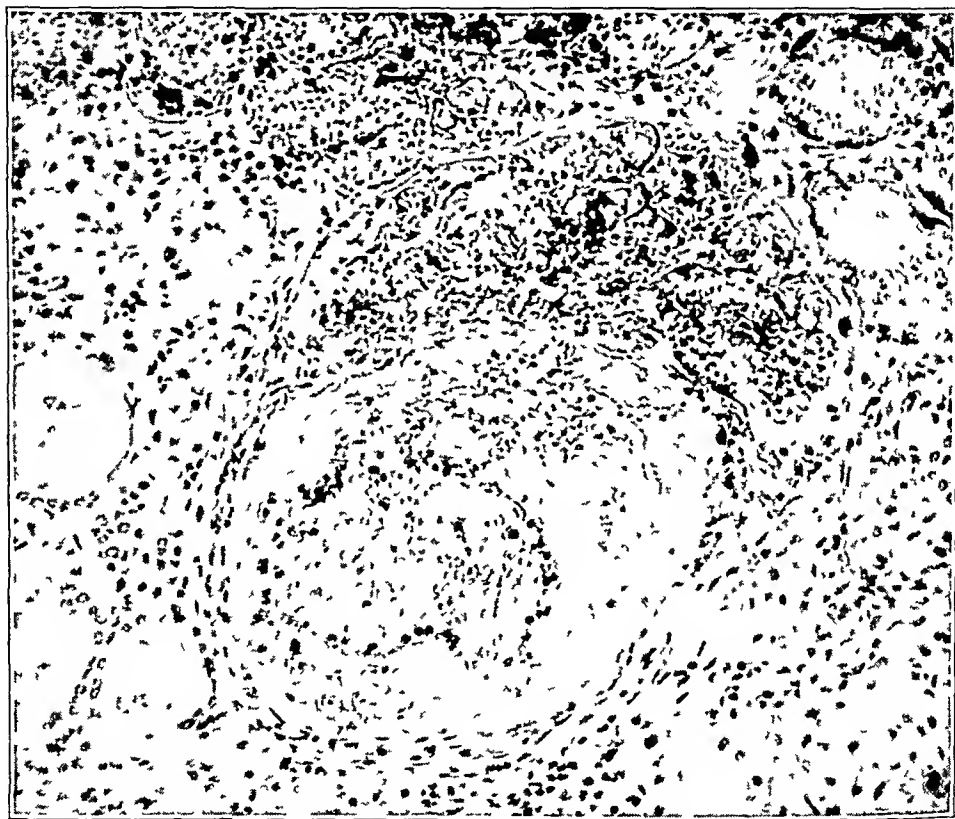


Fig 1—Thrombo-angioneclerosis with aneurysmal dilatation of the afferent vessel. The picture shows a crescent-shaped compressed glomerulus on top of the vessel. Zeiss objective A, eyepiece K20.

In addition to these triangular areas, other areas of necrosis were scattered through the deeper portions of the cortex and the medulla, which showed similar changes. These were narrow strips, perpendicular to the surface of the kidney.

The other changes found in the kidney pertained to the glomeruli, tubules and blood vessels.

The glomeruli, outside of the necrotic areas, were comparatively well maintained. There were numerous glomeruli with patent, blood-filled loops without any changes in their capsules. Other glomeruli, however, revealed homogenization of part of their tufts, the loops of which were apparently not permeable. The homogeneous material stained much more intensely with eosin than the rest of the



Fig 2—Necrosis of an interlobular renal artery with thrombosis (longitudinal section) Incomplete infarction of surrounding parenchyma Leitz apochromate 16 mm , eyepiece 4

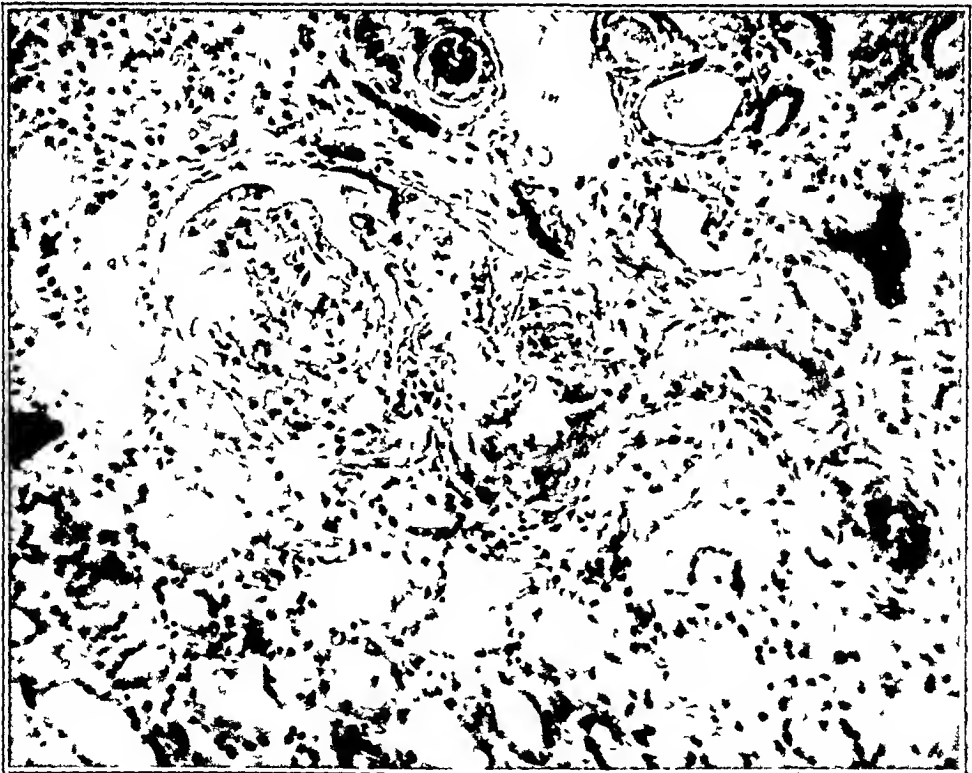


Fig 3—Necrosis of the afferent vessel with beginning dilatation partial necrosis of the glomerulus Polymorphonuclears are present in the necrotic areas Zeiss objective A , eyepiece K20



tissue In other glomeruli there was definite evidence of nuclear injury, in addition to the hyalinization The absence of endothelial cells and the presence of nuclear debris gave the impression of necrosis In such areas a few leukocytes were usually present

The tubular epithelium, outside of the necrotic areas, showed a great number of low cuboidal forms Most of the tubules were wide Some contained a homogeneous colloid material, which filled the whole lumen like a cast Others contained droplets of globular material, which was also homogeneous and tended to coalesce Casts were also found in the tubules of the medulla They were of the same colloid type Red cells were occasionally intermingled with the colloid material

The changes of the arteries were particularly impressive Both large and small arteries showed proliferation of the intima The newly formed cells were

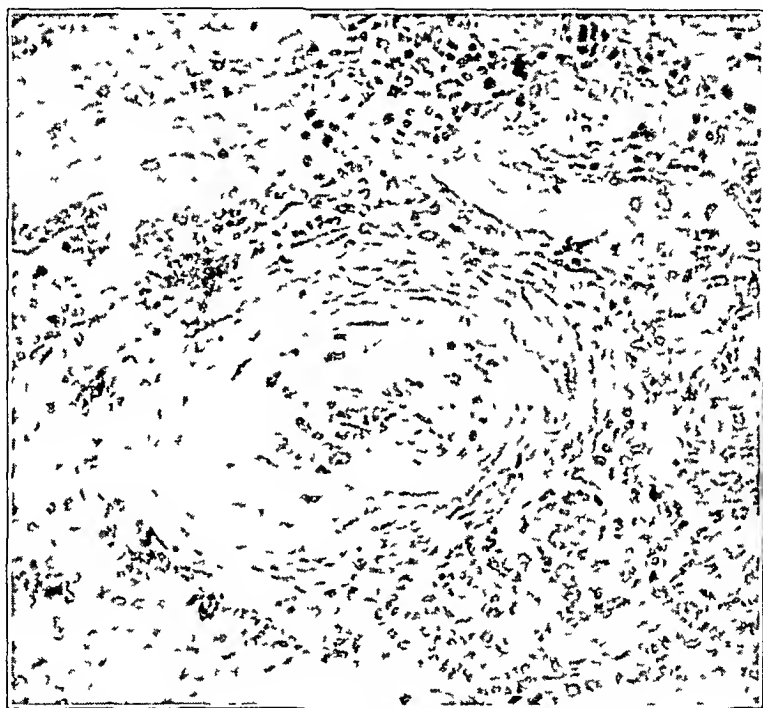


Fig 4—Obliterative endarteritis of an interlobular renal artery The absence of hyalinization and the presence of polymorphonuclears are to be noted Zeiss objective A, eyepiece K20

large and contained a great amount of lipid substance Hence, they appeared vacuolated The lumen of the arteries was considerably narrowed and frequently completely obliterated

The elastic fibrils were hyperplastic There was no doubling of the internal elastic membrane On the other hand, the old elastic membrane was occasionally interrupted, and the defect replaced by cellular proliferation The arterioles showed definite changes A number of these small vessels were transformed into homogeneous hyaline masses, which appeared on cross-section like intensely eosinophilic rings with a narrow lumen In others, the hyaline masses, replacing parts of the wall, alternated with granular debris, in which fragments of nuclei, particularly of polymorphonuclear leukocytes, were conspicuous Polymorphonuclears were found both in the lumen of these vessels and around their external surface

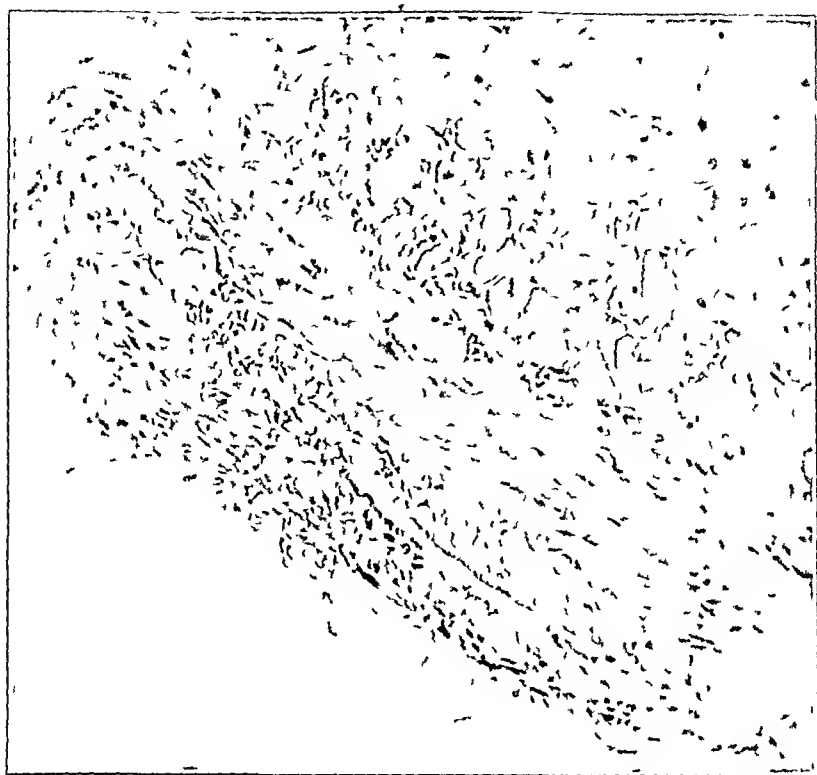


Fig 5—Subepicardial artery showing circumscribed focus of proliferation of intima and necrobiotic changes of the media Leitz apochromate 8 mm , eyepiece 4

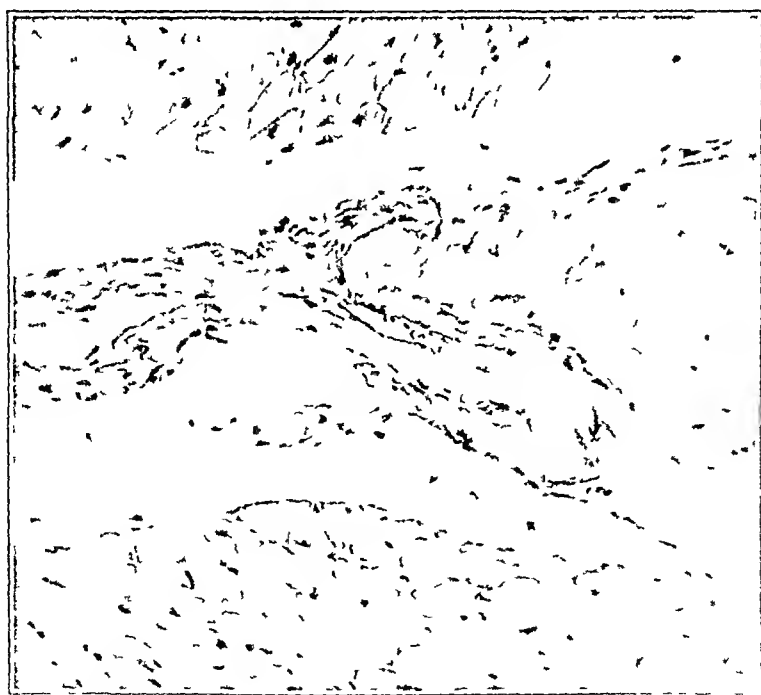


Fig 6—Myocardial artery showing extensive necrosis of the wall and partial obstruction of the lumen Leitz apochromate 8 mm eyepiece 4

Some of these arterioles could be followed to the glomeruli, the lesion continuing to the vasa afferentia, and then to the glomerulus proper, producing in the tufts the changes heretofore described. Some of the arterioles were thrombosed. The structure of the thrombus was granular or hyaline. Leukocytes could be seen within the thrombus. The wall of these arterioles was markedly necrotic.

The lesions of the arteries and arterioles were not restricted to the kidney. Other organs showed arterial lesions similar to those described, although somewhat less marked, namely, the spleen, the pancreas and particularly the myocardium.

Some of the smaller arteries of the heart showed nothing more than hyperplasia of the cells of the intima with eccentric narrowing of the lumen. Lipoidal deposits accounted for the vacuolization of these cells. The elastic membrane split about these areas, producing substantial defects. In other vessels, the proliferation was less marked, but there was evident necrosis of parts of the vessel

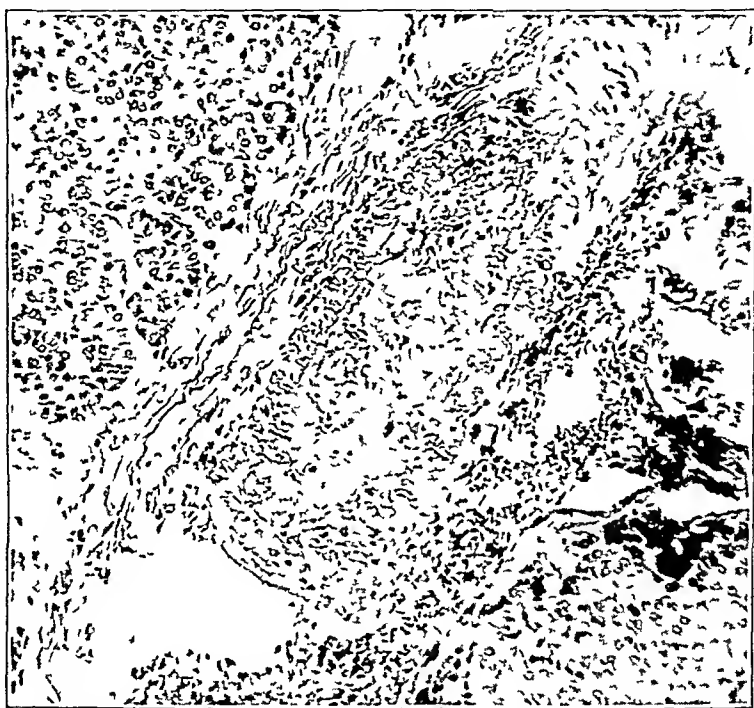


Fig 7—Pancreatic artery showing thrombosis with beginning organization, necrosis of the musculature and leukocytic infiltration. Leitz apochromate 8 mm, eyepiece 4.

wall, that is, homogenization, fragmentation of the fibrils and exudate, collected into granular lumps, disappearance of the nuclei by karyorrhexis or lysis and the appearance of polymorphonuclears. Some of the latter broke down, producing nuclear debris. Around some of these vessels, infiltration of the perivascular connective tissue by polymorphonuclears could be observed. Such infiltrations were particularly extensive in the intralobular stroma of the pancreas, adjacent to the pancreatic arteries, with lesions similar to those described.

#### COMMENT

The most significant features in this case were the changes in the blood vessels. These changes could be divided into two groups. The first group, representing apparently the older lesion, appeared to be

simply productive. These consisted of proliferation of the intima, with narrowing and occasionally occlusion of the lumen. The outer coats of the vessels were also involved. There was considerable production of collagenous fibrils in the adventitia, and a loss of musculature in the media with substitution of connective tissue. The elastic elements were also involved. There was a splitting up of the internal elastic fibrils. Deposits of lipoids in the cells of the proliferated intima were abundant. Necrosis or calcification was not a feature of the process, nor was hyalinization of the thickened intima. Thus, the changes resembled more those of chronic inflammation than those of arteriosclerosis.

The changes in the other group were much more recent. They were essentially alterative, including, as they did, necrosis and hyalinization. Acute exudative inflammatory changes, such as the migration of leukocytes and the appearance of an albuminous exudate, were concomitant. Thrombosis of some of the capillaries and arterioles completed the picture.

These changes were especially characteristic and were essentially different from the secondary changes of the glomeruli in ordinary arteriosclerosis. The difference was sufficient to justify the assertion that the pathogenesis of these lesions was also different. This contention was substantiated by the changes in the arteries outside of the kidneys which were of the same character as those observed in the renal arterioles and capillaries. The changes of the glomeruli, moreover, were practically identical with what has been described repeatedly in cases of severe toxic and septic conditions and interpreted as a toxic or bacterial focal glomerulonephritis. The focal distribution of such lesions is their chief characteristic in contrast with the ordinary glomerulonephritis, in which all the glomeruli and every loop of each glomerulus is involved. The inflammatory character and the toxic or bacterial pathogenesis of these lesions are well established.

It therefore seems that the lesions in this case are entitled to the same interpretation. The presence of the chronic endarteritic changes with subsequent lesions of the kidney do not contradict the statement.

The main question is whether the more acute focal lesions occurred simply incidentally with the chronic vascular condition or whether they were dependent on the latter. It is conceivable that a preceding disease of the arterioles was responsible for the focus of minor resistance which facilitated the onset of the acute lesion. On the other hand the inflammatory character of the chronic arteriolar changes suggests the possibility that both the chronic lesion and the acute lesion were due to the same or similar causes, the acute changes representing an exacerbation of the chronic process.

In fact, cases of the type reported here usually occur in much younger persons than do cases of ordinary arteriosclerosis. The age of the patient was 18, and the material on which this study is based includes a case in a patient aged 21, and two cases in patients less than 30. According to Fahn's statistics, persons subject to ordinary arteriosclerosis are above 50 years of age, and the majority are above 60. The patients to whom he refers as having malignant sclerosis die at an age below 60 and almost one third of them die before 40. The predisposition of younger persons toward this condition is a strong argument against the conception that it is only a complication of ordinary arteriosclerosis. One is justified in disconnecting such cases of so-called malignant sclerosis from the ordinary arteriosclerosis. As a suitable name for this condition, I suggest the term renal thrombo-angioneclerosis or, in cases of advanced contraction of the kidneys, angioneclotic nephrosclerosis.

#### SUMMARY

1 One of a group of cases has been described in which the characteristic feature is endarteritis with necrosis of the vessel wall, and subsequent changes in the renal parenchyma.

2 The vascular changes are not restricted to the kidney, but are also found in vessels of the other organs of the body.

3 Clinically, these cases are characterized by a comparatively rapid development of renal insufficiency. Changes of the eyegrounds are conspicuous.

4 The condition is found in young or middle aged persons in contradistinction to cases described as arteriosclerotic nephrosclerosis.

5 The following nomenclature is suggested: renal thrombo-angioneclerosis for the more acute form and angioneclotic nephrosclerosis for cases of longer duration.

# TOXIC CIRRHOSIS OF LIVER DUE TO CINCHOPHEN<sup>\*</sup>

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CLEVELAND

Cinchophen is widely regarded as a drug of low toxicity Sollmann<sup>1</sup> gave no warning against long continued massive doses, and the general practice is to maintain saturation over long periods Graham<sup>2</sup> and others in England and Germany recommended that the drug be given for a period of about four days and discontinued for a similar interval It is maintained that this procedure produces maximum beneficial effects without danger My purpose in this paper is to report two fatal cases of cirrhosis of the liver apparently due to prolonged and massive administration of cinchophen

In 1922, Schroeder<sup>3</sup> first drew attention to the toxic effects of cinchophen and published a review of seventeen cases Since then twenty-eight cases have been found in the literature In this country, Rabinowitz<sup>4</sup> and Sutton<sup>5</sup> have drawn attention to the toxicity of this drug The principal symptoms are headache, gastro-intestinal disturbance and icterus

There is little doubt but that natural idiosyncrasy may be of importance Evans'<sup>6</sup> patient took only 15 grains (0.97 Gm) of the drug In other cases the amounts ranged from 80 to 4,000 grains (5.2 to 260 Gm) over variable periods The symptoms, as a rule, appear late in the course of treatment It is also thought that idiosyncrasy may be artificially induced Worster-Drought's<sup>7</sup> patient, after having taken 370 grains

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<sup>\*</sup> Submitted for publication, Feb 15, 1929

<sup>\*</sup> From the Department of Pathology, Cleveland City Hospital and School of Medicine, Western Reserve University

1 Sollmann, T A Manual of Pharmacology, ed 3, Philadelphia, W B Saunders Company, 1926

2 Graham, G Presidential address, Section of Therapeutics and Pharmacology, Royal Society of Medicine, October, 1926, quoted from Loewenthal, Macay and Lowe Brit M J **1** 592, 1928

3 Schroeder, K Cases of Cinchophen Poisoning, Ugeskr f Laeger **84** 1141 (Sept 7) 1922, quoted from Loewenthal, Macay and Lowe Brit M J **1** 592, 1928

4 Rabinowitz, M A Toxic Hepatitis and Hepatolysis Following Use of Atophan, M Clin N Amer **11** 1025, 1928

5 Sutton, D Acute Yellow Atrophy of the Liver Following the Taking of Cinchophen, J A M A **91** 310 (Aug 4) 1928

6 Evans, G Discussion, Brit M J **2** 689 (Oct 16) 1926

7 Worster-Drought, C Atophan Poisoning, Brit M J **1** 148 (Jan 27) 1923

(25.05 Gm) in twelve days, developed urticaria, which disappeared when the medication was stopped. One dose of  $7\frac{1}{2}$  grains administered three weeks subsequently brought on urticaria, gastro-intestinal disturbance and jaundice, which lasted ten days.

A dangerous aspect of cinchophen poisoning is the late and relatively abrupt onset of the symptoms. In the fatal case reported by Willcox,<sup>8</sup> the first signs of poisoning appeared at the completion of the treatment. In one of Loewenthal's<sup>9</sup> fatal cases jaundice developed two weeks after the medication had been stopped. Immediate reactions have been observed only on the intravenous use of the cinchophen derivative, diodoatophan, containing about 50.7 per cent of iodine.

The most frequent symptom is jaundice. It developed in every case except those of Phillips<sup>10</sup> and Herrick,<sup>11</sup> which were very mild and showed only a rash. Vomiting, anorexia, heart burn and diarrhea, though not seen in every case, when present usually appear before the jaundice. The cinchophen rashes are either of the scarlatiniform type or are urticarial, there may also be petechial manifestations of the skin. In the later stages of the toxicosis the typical signs and symptoms of advanced destruction of the liver occur, namely, purpura, restlessness or coma, high icteric index, urobilin and tyrosin in the urine. The stools may be acholic. If the patient survives, cirrhotic changes occur which may lead to a diminution of liver volume and to an interference with the portal circulation. Damage to the kidney has been demonstrated clinically and is proved by the results of several autopsies. The clinical picture, therefore, is mainly one of serious damage of the liver, and it is probable that this accounts for all the symptoms, including the late skin rashes.

The seven autopsies that I have found recorded and those on my cases substantiate this hypothesis. In every case there was evidence of an "hepatitis" or of a degeneration of the parenchyma of the liver. Singer's<sup>12</sup> case showed only abundant round cell infiltration. The others all revealed more or less extreme fatty metamorphosis with or without periportal fibrosis. In some cases there was proliferation of the bile ducts. The livers were all small, with the exception of that in my first case, and ranged in weight from 500 to 1,150 Gm. A nephrosis,

8 Willcox, W. H. Atophan Derivatives in Rheumatism, *Brit. M. J.* **2** 273 (Aug. 7) 1926.

9 Loewenthal, L. J. A., Macay, W. A., and Lowe, E. C. Two Cases of Yellow Atrophy of the Liver Following the Administration of Atophan, *Brit. M. J.* **1** 592 (April 7) 1928.

10 Phillips, J. Skin Rashes Following the Administration of Atophan, *J. A. M. A.* **61** 1040 (Sept. 27) 1913.

11 Herrick, W. W. A Scarlatiniform Rash from Atophan, *J. A. M. A.* **61** 1376 (Oct. 11) 1913.

12 Singer, S. Discussion, *Wien klin. Wchnschr.* **40** 238, 1927.

with damage particularly to the convoluted tubules, was noted in four cases

Loewenthal<sup>9</sup> spoke of a subacute nephritis Rake<sup>13</sup> mentioned hemorrhages in the suprarenal glands There have been ten fatalities in the forty-six cases, and nine have come to autopsy Two of the poisonings were due to the cinchophen derivative diodoatophan Twelve deaths are reported in Loewenthal's<sup>9</sup> survey, but I do not include them since he does not give the references

#### REPORT OF CASES

CASE 1—A white woman, aged 20, in January, 1928, developed an acute arthritis which affected almost all the joints She was in bed for three months, and in May a tonsillectomy was done One week following this operation, the patient became jaundiced and developed high fever and diarrhea The gastrointestinal disturbances lasted six weeks In June, the patient recovered and was able to walk about A second attack of arthritis intervened which lasted up to the time of admission to the City Hospital On Aug 14, 1928, her physician found that she had an evening fever of 102 F She was also suffering from severe nosebleeds and from hemorrhages around the gums On August 19, she was admitted to a Cleveland hospital for various roentgen examinations and observations on the blood, which all proved negative On September 9, the patient became worse The temperature was 103 F There was vomiting, diarrhea, pain in the right side of the chest and apathy She was admitted to the City Hospital, Cleveland, on Sept 13, 1928 She was emaciated and listless The skin was dry and hot There was a maculopapular eruption on the face, moderate pallor and hemorrhage from the nose and gums The heart rate was 88, the blood pressure was 90 systolic and 52 diastolic, and the liver was palpable 3 or 4 cm below the costal margin The spleen was firm and easily felt There was no evidence of bone or joint disease at that time The urine contained a trace of albumin The Wassermann reaction was negative Examinations of the blood showed a severe anemia (2,080,000 red blood cells and 46 per cent hemoglobin, Sahli) and a rather high platelet count of 800,000 There were 12,240 leukocytes, of which 78 per cent were polymorphonuclears The stool did not contain typhoid bacilli Blood cultures were negative on two occasions The Widal test was negative, and urine cultures gave no growth The joints became swollen again, pneumonia developed The temperature dropped to subnormal in the last two days, and the pulse rate rose to 120 The patient died on Sept 18, 1928 The patient's first physician had given her cinchophen in January The exact amount could not be ascertained but it is probable that she had at least as much as was given to her by her second physician, namely, 80 tablets of cinchophen of 7½ grains (487 Gm) each and, in addition, 40 tablets of oxyiodide, which is a combination of iodine and cinchophen In the City Hospital she had been given at least 60 grains (39 Gm) of cinchophen

At autopsy the body appeared poorly nourished There were ecchymoses and petechiae beneath the skin The skin was of a light lemon color The heart was normal There was confluent bronchopneumonia of the lower lobes of both lungs and the upper lobe of the right lung, which had progressed to abscess formation

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13 Rake, G W A Case of Subacute Yellow Atrophy Following the Taking of Atophan, *Guy's Hosp Rep* 77 229, 1927



The liver weighed 1,950 Gm and extended 4 cm below the inferior costal margin. The capsular surface was uneven and showed projecting, irregular, firm, mustard yellow areas. With the knife a fatty fluid was expressed from the liver tissue. The bile ducts were patent. The spleen weighed 325 Gm and was the seat of acute hyperplasia. The kidneys weighed 325 Gm, in one there were several cortical abscesses. The cortices of both kidneys were distinctly yellow. Microscopic sections showed the following conditions. The cytoplasm of practically all of the liver cells was occupied by many vacuoles of varying sizes which sudan III fat stain showed to be fat. What was left of the cytoplasm was granular. The sinusoids were dilated. There was an enormous amount of connective tissue in the portal spaces which contained a large number of small round cells and some hemorrhage. Islands of liver tissue were cut off or entirely replaced by connective tissue. There was a definite proliferation of the bile ducts. Sudan

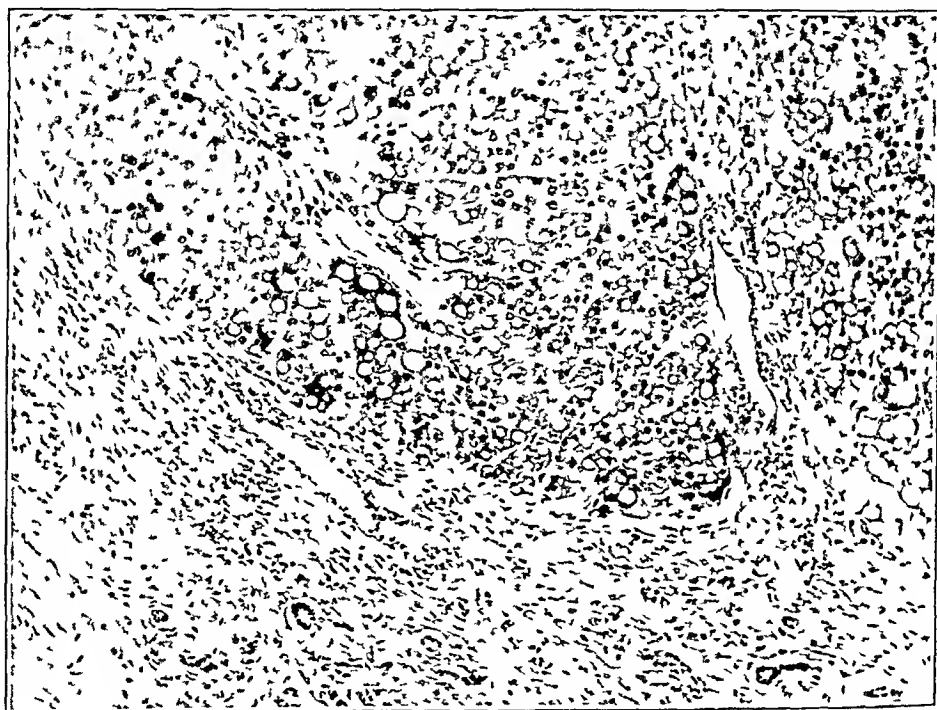


Fig 1 (case 1) —Photomicrograph (100 diameters) showing fatty degeneration of liver cells and increase of connective tissue

III fat stain showed an extensive accumulation of fat in the basal portions of the cells of the convoluted tubules of the kidney. Fat was also present but more diffusely in the epithelium of the collecting tubules. The epithelium of the tubules showed severe retrogressive changes which in part had led to a complete loss of cytoplasm and nuclei. Many of the collecting tubules contained nothing but fibrillar substance and a homogeneous pink-staining material. The subcapsular space of the glomeruli was occupied here and there by a pink granular material. One section showed a sharply defined necrosis of the parenchyma and interstitial tissue beneath the capsule. About this area there was a zone of fibroblast proliferation. The connective tissue was not increased elsewhere in the kidney. The heart showed no abnormalities.

Since the autopsy was done within eight hours of death the observations on the kidney were of importance. The liver was examined for phosphorus by

Dr H H Beard of the department of biochemistry of Western Reserve University Mitscherlich's test showed that no phosphorus was present The pathologic diagnosis, therefore, was confluent bronchopneumonia of the lung with abscess formation, abscess of the kidney, fatty degeneration of the kidney, toxic cirrhosis of the liver and acute splenic hyperplasia

CASE 2—A white woman, aged 46, had been treated in the City Hospital Dispensary for arthritis over a period of three years Cinchophen had relieved the pain, and the drug had therefore been repeatedly administered The dose had been 15 grains (0.97 Gm) from three to four times a day, over briefer periods of time  $7\frac{1}{2}$  grains had been given In 1926, the total amount taken was 3,150 grains (204.75 Gm), in 1927, 2,100 grains (136.50 Gm), and in 1928 up to the onset of the fatal illness, 1,800 grains (117.40 Gm) The Wassermann reaction of the blood was negative

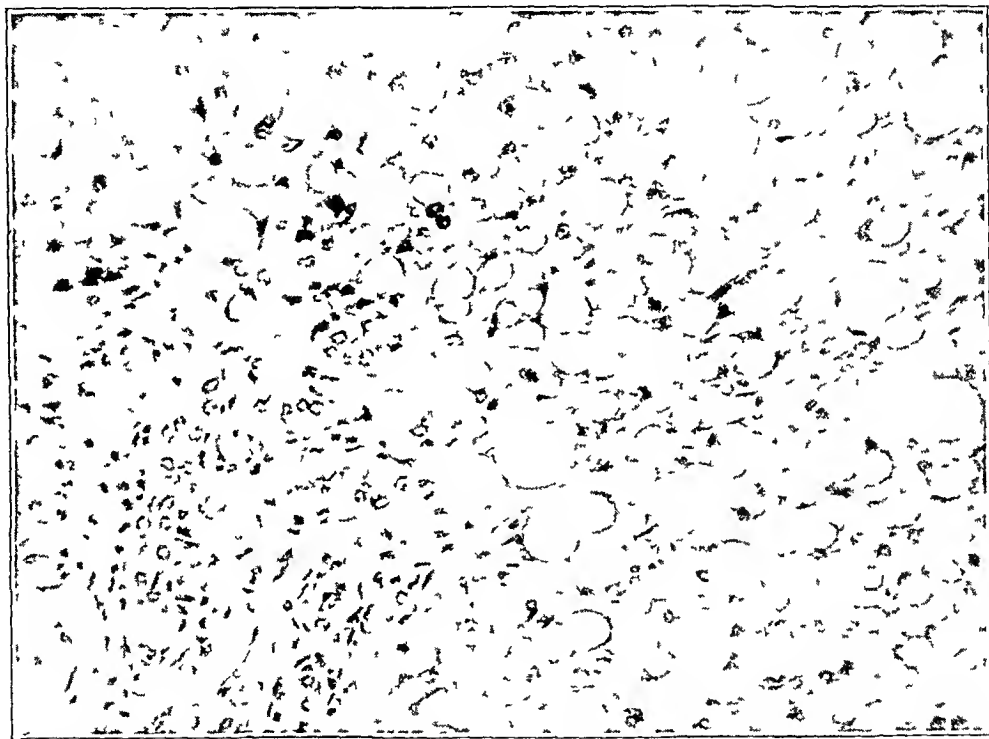


Fig 2 (case 1) —Photomicrograph (200 diameters) showing fatty degeneration of liver cells, proliferation of bile ducts and young connective tissue

On November 17, the patient returned to the Dispensary of the Cleveland City Hospital For three weeks she had noticed that pain and tenderness in the epigastrium ("stomach trouble") followed the ingestion of the cinchophen The dosage during this time had been  $7\frac{1}{2}$  grains four times daily The patient felt weak and complained of "nervousness" The skin was icteric and showed a rash, the eyelids were puffy, and she had gained 6 pounds (2.7 Kg) in about six weeks The urine contained large quantities of bile pigment and a few casts. The temperature was normal

The patient was admitted to the hospital on November 21 The epigastric pain had ceased, but the icterus was worse and nausea and vomiting had set in She was confused, apprehensive and at times semicomatose The admitting physician ascribed her mental condition to an injection (morphine?) which had been given by a private physician for the severe epigastric pain However, the disorientation

and stupor increased. There were twitchings of the muscles of the arms and face, and on the sixth day generalized convulsions set in. The breath had an acetone odor, the spleen was not palpable and on percussion the liver dulness was found high above the costal margin. The Babinski and Oppenheim reflexes and ankle clonus were present bilaterally. The temperature rose to 39 C (102.2 F), and the patient died in coma with the signs and symptoms of pulmonary edema on the sixth day of her hospital stay.

The total urinary output was never more than 300 cc, and the urine was strongly positive for bile and contained granular casts, white blood cells and albumin. On the day of admission, the chemical examination of the blood gave the following results: sugar, 108 mg per hundred cubic centimeters, carbon dioxide (saturation volume), 27 per cent, whole blood chlorides, 474 mg per hundred cubic centimeters, and urea nitrogen, 27 mg per hundred cubic centi-

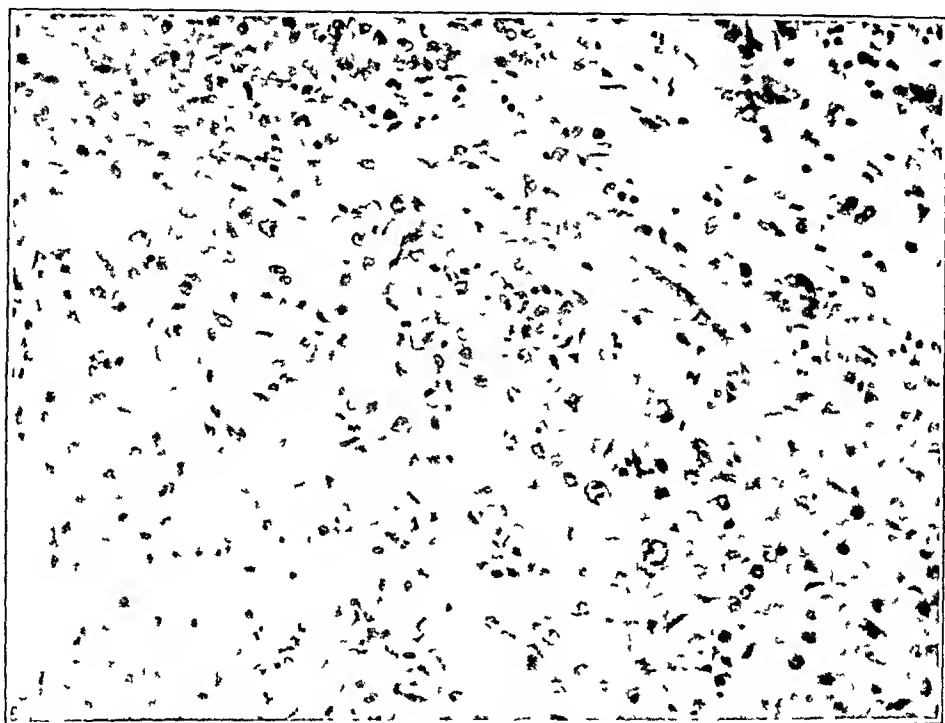


Fig 3 (case 2) —Photomicrograph (300 diameters) showing fatty degeneration and hyalinization of liver cells, proliferation of bile ducts and increase in connective tissue

eters. The next day the icteric index was determined and found to be 80. On the third day, the plasma chlorides were 563 mg per hundred cubic centimeters, and the carbon dioxide saturation volume was 37 per cent. On November 23, the white blood cell count was 11,000, the hemoglobin (Sahli), 85 per cent.

Autopsy was done four hours after death. The body was obese and very icteric, and the skin showed a papular eruption over the chest and extremities. Petechiae were found on the skin and in the mucous and serous membranes. The liver weighed only 575 Gm. Its surface was nodular, individual yellow nodules, which were about 1 mm in diameter, were separated by a red, firm tissue. On cut section, irregularly formed islands of soft yellow tissue were found in a mass of red and firmer tissue. The gallbladder contained a normal amount of thin bile and a few cholesterol stones. The two kidneys together weighed 400

Gm They were pale and the surface was smooth, on cut section, the tissue bulged and the normal architecture was indistinct. The pyramids were streaked with yellow. There was an increase in peripelvic fat. The stomach contained a coffee-ground material, and the mucosa of the entire gastro-intestinal tract was hyperemic.

The histologic observations were as follows. The myocardial fibers stained poorly. A fat stain (sudan III) revealed an extensive fatty degeneration of the muscle fibers. The epithelium of the tubules of the kidney was swollen and granular. Sudan III stain showed the presence of an enormous amount of intracellular fat. Here and there in the liver a few islands of liver tissue were found in a mass of young connective tissue which was infiltrated by many small round cells. The bile ducts had proliferated to a remarkable degree. The liver tissue

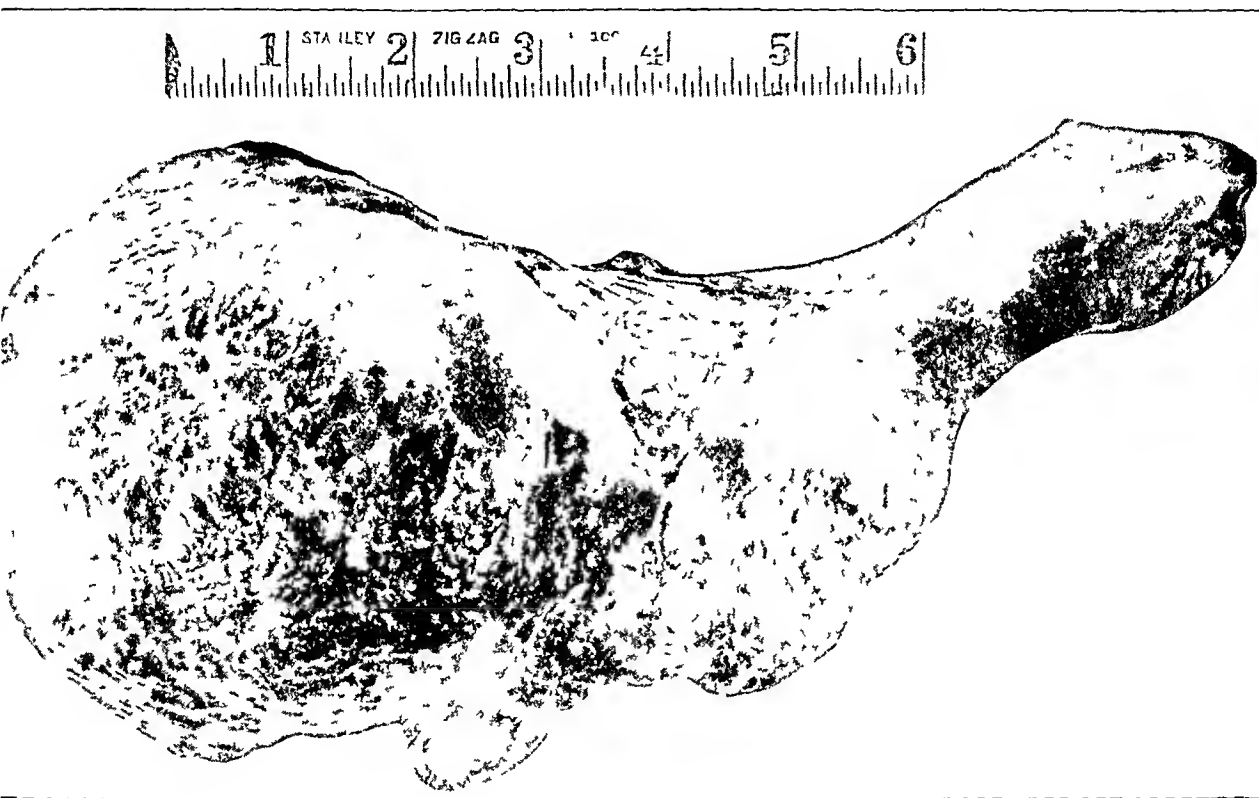


Fig 4 (case 2) —Photograph of liver to show the size (scale in inches) and nodular surface

that was left was in a state of cloudy swelling, vacuolization or hyalinization. Hardly one normal cell could be found. There was extensive hemorrhage into the masses of necrotic cells. The sudan III stain demonstrated free fat in all these cells. The rest of the organs, spleen, pancreas, lung and uterus, showed chronic passive hyperemia.

The pathologic diagnosis, therefore, was toxic cirrhosis of the liver, fatty degeneration of the myocardium and kidney, and passive hyperemia of all organs.

It is probable that there are many more cases of toxemia due to cinchophen than one is aware of. At a conference in the City Hospital at which one of my cases was presented, several physicians reported that they had seen jaundice during the period of medication with

cinchophen The first sign of gastro-intestinal disturbance should therefore be an indication for stopping the drug Jaundice must be regarded as a symptom of serious damage to the liver The cases of Willcox<sup>8</sup> and Loewenthal<sup>9</sup> in which no legitimate precaution had been neglected raise the question as to whether or not the use of cinchophen is of such great value that it warrants the danger Willcox's patient had had only 85 grains (5.52 Gm), Loewenthal's patient had been treated according to the Graham method In both cases the symptoms set in after the medication had already ceased The experience of those who have used the cinchophen derivative, duodoatophan, proves that cinchophen given in one large dose may produce the same damage as when given in smaller doses over long periods of time The number of cases already reported is sufficiently great to eliminate the probability of mere coincidence

#### CONCLUSION

Forty-seven cases of cinchophen toxicosis have been published<sup>14</sup> Ten deaths have resulted In all cases there is evidence of serious damage of the liver Every patient who receives cinchophen should be observed for gastro-intestinal symptoms, rashes or icterus and the occurrence of such symptoms should be the immediate indication for stopping the use of the drug The therapeutic use of cinchophen may well be reevaluated in reference to its harmful properties

I am indebted to Dr Howard T Karsner for taking the photomicrographs which illustrate this article

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<sup>14</sup> De Rezende recently published a case (*Brasil-med* **41** 1005 [Sept 24] 1927), and Motzfeldt described a case of icterus due to cinchophen, *Norsk Mag f Laegevidensk*, March 21, 1929, p 283

# THE PNEUMOTACHOGRAPH IN CERTAIN INTRATHORACIC DISEASES

ITS DIAGNOSTIC VALUE <sup>†</sup>

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AND

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## INTRODUCTION

The close functional and anatomic relationship between the heart and lungs is well recognized. Disturbance in the normal functions of the lungs may have considerable importance in diseases of the heart and blood vessels. Occasionally, respiratory changes are the first recognizable signs of circulatory failure. It is partly for this reason that, in the past, the respiration has been studied carefully with the aid of a number of technical devices. The excursions of various parts of the thoracic wall have been registered. Similarly, volumetric measurements of the ventilation have received careful consideration. Through the earlier investigations of Bergeon and Kastus,<sup>1</sup> Rosenthal,<sup>2</sup> Gad,<sup>3</sup> Ewald<sup>4</sup> and Gevers-Leuven,<sup>5</sup> and through the more recent studies of Pech<sup>6</sup> and Beyne,<sup>7</sup> it has become an established fact that the velocity of the respired air is also of considerable importance in the mechanism of the respiration. Recently, Fleisch<sup>8</sup> described an apparatus which registers the

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<sup>†</sup> Submitted for publication, Dec 26, 1928

<sup>†</sup> From the Thorndike Memorial Laboratory of the Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, and the Department of Medicine, University of Leipzig, Germany

1 Bergeon, L., and Kastus, C. Nouvel appareil enregistreur de la respiration, *Gaz hebdomadaire de medecine*, 1868, vol 579

2 Rosenthal, J. Die Physiologie der Atembewegungen, in Hermann. Handbuch der Physiologie, Leipzig, F. C. W. Vogel, vol 4, chap 2, p 223

3 Gad. Einige kritische Bemerkungen die Pneumotachographie betreffend, *Archiv für Anatomie und Physiologie* **2** 553, 1879

4 Ewald, I. R. Der normale Atmungsdruck und seine Kurve, *Archiv für die gesammte Physiologie* **19** 461, 1879

5 Gevers-Leuven. Contribution a l'aerodynamique des voies respiratoires, *Untersuchungen aus dem physiologischen Laboratorium*, Utrecht, 1904

6 Pech, S. L. La notion du debit respiratoire maximum, mesure pratique de ce debit au moyen du moyen manometrique, *Presse medicale* **29** 93, 1921

7 Beyne, J. L'etude graphique du debit respiratoire au moyen du masque de Pech, *Presse medicale* **31** 698, 1923

8 Fleisch, A. Der Pneumotachograph, ein Apparat zur Geschwindigkeitsregistrierung der Atemluft, *Archiv für die gesammte Physiologie* **209** 713, 1925

velocity curve of the inspired and expired air. The velocity curve is an expression of the differential quotient of the respiratory volume over time. Fleisch's pneumotachograph consists of ninety tubes each 20 cm long and 2 cm in diameter. The resistance offered by the tubes when the subject is breathing through the mouth piece, and the fall in pressure between the two ends of the tubes, are functions of the velocity of the inspired air. Although the resistance offered the tubes of the apparatus is not sufficient to cause an alteration of normal respiratory movements, the dead space is rather undesirable.

#### APPARATUS

The pneumotachograph used in this study has been described by one of us.<sup>9</sup> The instrument is based on the following principle. If a fluid or gas flows through a tube, the diameter of which changes suddenly from narrow to wide, the stream does not fill the first portion of the wider tube instantly, the pressure may be considerably lower here than in the narrower portion of the tube. If a small ring is fitted within a cylindric tube, during the passage of the air through the tube there is a difference in pressure between the two sides of the ring. This difference in pressure may be expressed in the following formula

$$h = \frac{U}{2g} \left( \frac{F_2}{F_1} - 1 + \frac{1}{3} \right)$$

if  $h$  represents the difference in pressure,  $U$  the velocity of flow of the air,  $g$  the gravity of the earth,  $F_1$  the diameter of the inserted resistance,  $F_2$  the diameter of the tube and  $J$  the coefficient which is determined empirically. According to this formula, the difference in pressure is proportional to the velocity of the flow of air and to the degree of resistance. This principle receives, then, the following practical application in the apparatus.

In the middle portion of a metal tube, 5 cm long, a ring is placed. The relation between the width of the ring and the diameter of the tube is 1:7. The ring inserted offers a resistance to the stream of air entering into the metal tube, a difference in pressure is therefore created between the two sides of the ring. This difference in pressure is proportional to the velocity of the stream of air. Therefore, if this difference in pressure is registered with a differential capsule, which is then empirically calibrated to a number of currents of gas of known velocity, the curve obtained gives a direct measure of the velocity of the current of air. For the registration of the differences in pressure, a sensitive modified Frank differential capsule is used. A small mirror attached to the membrane reflects a small narrow beam of light on a moving film. The connection between the respiratory tube  $R$  (fig 1) and the differential capsule  $D$  (fig 1) is established with two short rubber tubes,  $A_1$  and  $A_2$  (fig 1). The distance from the opening of these tubes into the respiratory tube to the metal ring inserted into the tube is equal on both sides. For quantitative calibration, the apparatus is inserted between a gas tank and a gasometer, and standard curves are obtained with streams of gas of known velocity.

<sup>9</sup> Hochrein, M. Ueber Pneumotachographie, Arch f d ges Physiol **219** 753, 1928

The curves obtained with the apparatus represent the differential quotient between the time and volume of respiration. If the curve is represented on cartesian coordinates, the abscissa of which represents the time, and the ordinate the velocity of the respired air, the volume of respiration can be obtained if the surface area that is enclosed by the curve and abscissa is measured with a planimeter. Preliminary heating of the respired air, required when the Fleisch apparatus is applied, is not necessary. The resistance of the apparatus is minimal, and the dead space is small, owing to the fact that the respiratory tube is short. The apparatus can be used in experiments on animals, in that case a small respiratory tube is inserted into the trachea.

The apparatus thus enables one to measure simultaneously (a) the duration of inspiration and expiration, (b) the maximal, minimal

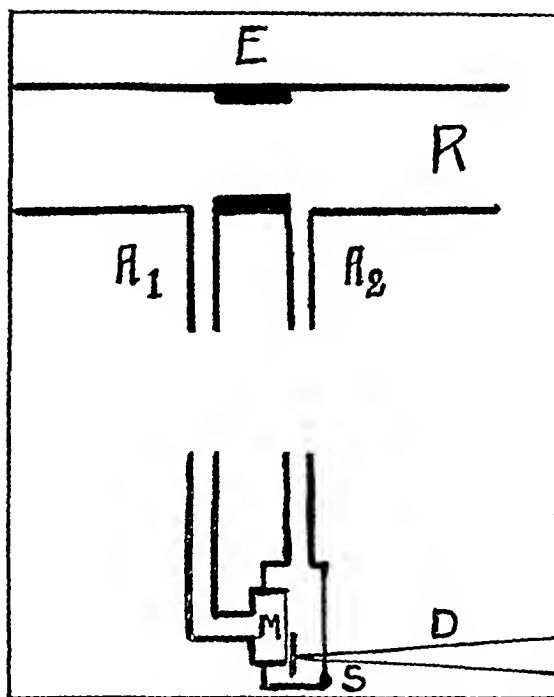


Fig 1—Diagram of the pneumotachograph used. *R* is the respiratory tube, *D* the differential capsule, *E* the narrow portion of the tube, *M* the Frank capsule, *S* light to mirror.

and mean velocity of the expired air, (c) the volume of a single respiration, (d) the rate of respiration, and (e) the respiratory minute volume.

Figure 2 represents the pneumotachogram (*P*) of a normal subject, with the simultaneously registered heart sounds (*S*), electrocardiogram (*E*) and velocity curves for the pulse (*V*). In analyzing the pneumotachograms of normal persons, one finds that there are small irregularities superimposed on the inspiratory and expiratory curves. These irregularities have been noted by previous investigators. Fleisch<sup>8</sup> attributed them to fluctuation in the velocity of respired air, as a result of uneven function of the respiratory muscles. That at least some of the fluctuations in the velocity do not depend on the function of the respiratory muscles, but have a relationship to the cardiac function, can



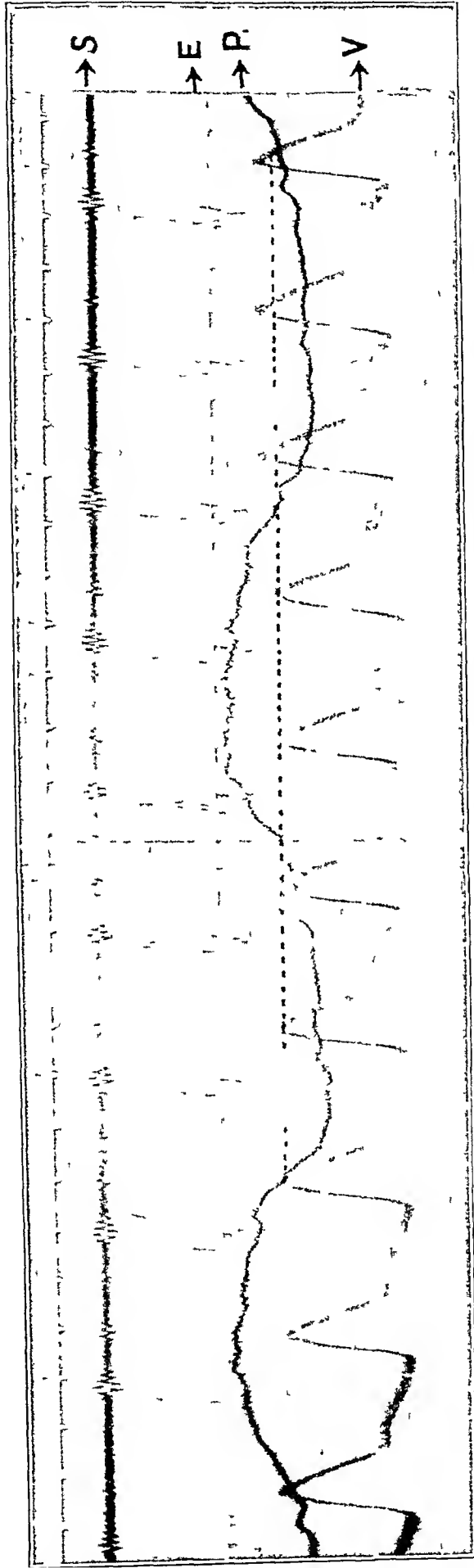


Fig 2.—Pneumotachogram (*P*) of a normal subject with simultaneously registered heart sounds (*S*), electrocardiogram (*E*) and velocity curves of the pulse (*V*)

be demonstrated if one simultaneously registers the heart sounds or cardiac action (electrocardiogram) with the pneumotachogram. If the respiration stops, the pneumotachogram continues as a straight line, in normal persons, and no notches are observed.

In extending our observations from normal subjects to patients with cardiovascular and pulmonary diseases, it was found that some of the patients showed notchings of the pneumotachograms even during respiratory standstill. These notchings were present in inspiratory standstill only in some of the patients observed, and in both inspiratory and expiratory standstill in others. It was also observed that certain simple respiratory gymnastics intensified or decreased these notchings of the curves. It was our aim, therefore, to determine the mechanisms and the significance of the presence and absence of these notchings of the pneumotachograms.

#### EXPERIMENTAL OBSERVATIONS

After a number of attempts, the following experiment was performed on normal subjects and on patients studied. The pneumotachogram and electrocardiogram, or the heart sounds, were registered simultaneously during the natural state of the respiration. Then the subject took a deep inspiration, followed by a respiratory standstill of six seconds' duration, a forcible expiration followed, with another respiratory standstill of six seconds' duration at the end of the expiration. In registering the normal respiration and the described respiratory gymnastic of fifty normal subjects, no definite notchings synchronous with the heart action during the respiratory standstill were observed. The tracing continued as a straight line during respiratory standstill.

Figure 3 represents such an observation, with simultaneously registered heart sounds, electrocardiogram and velocity curve of the pulse. With the onset of respiratory standstill at the end of a forceful inspiration, the tracing falls to the zero line and forms a straight line until the respiration is resumed. Occasionally, irregularities occur during the respiratory standstill. These, however, have no relation to the function of the heart, and are due either to swallowing movements or to the fact that a number of elderly persons are unable to hold their breath completely, even if the extrathoracic muscles stop their activity. Slight excursions of the diaphragm continue. It is also important that during the respiratory standstill the vocal cords should be kept open, for if closed, the pneumotachogram will always show a straight line.

The eighty-three patients whose respirations were studied had the following conditions: valvular disease of the heart, (a) ten cases of syphilitic origin and (b) twenty-five cases resulting from rheumatic fever, syphilitic aneurysm of the aorta, six cases, arterial hypertension with myocardial hypertrophy, twenty-one cases, adhesive pericarditis, four cases, tumors of the lungs and of the pleura, seven cases, and other

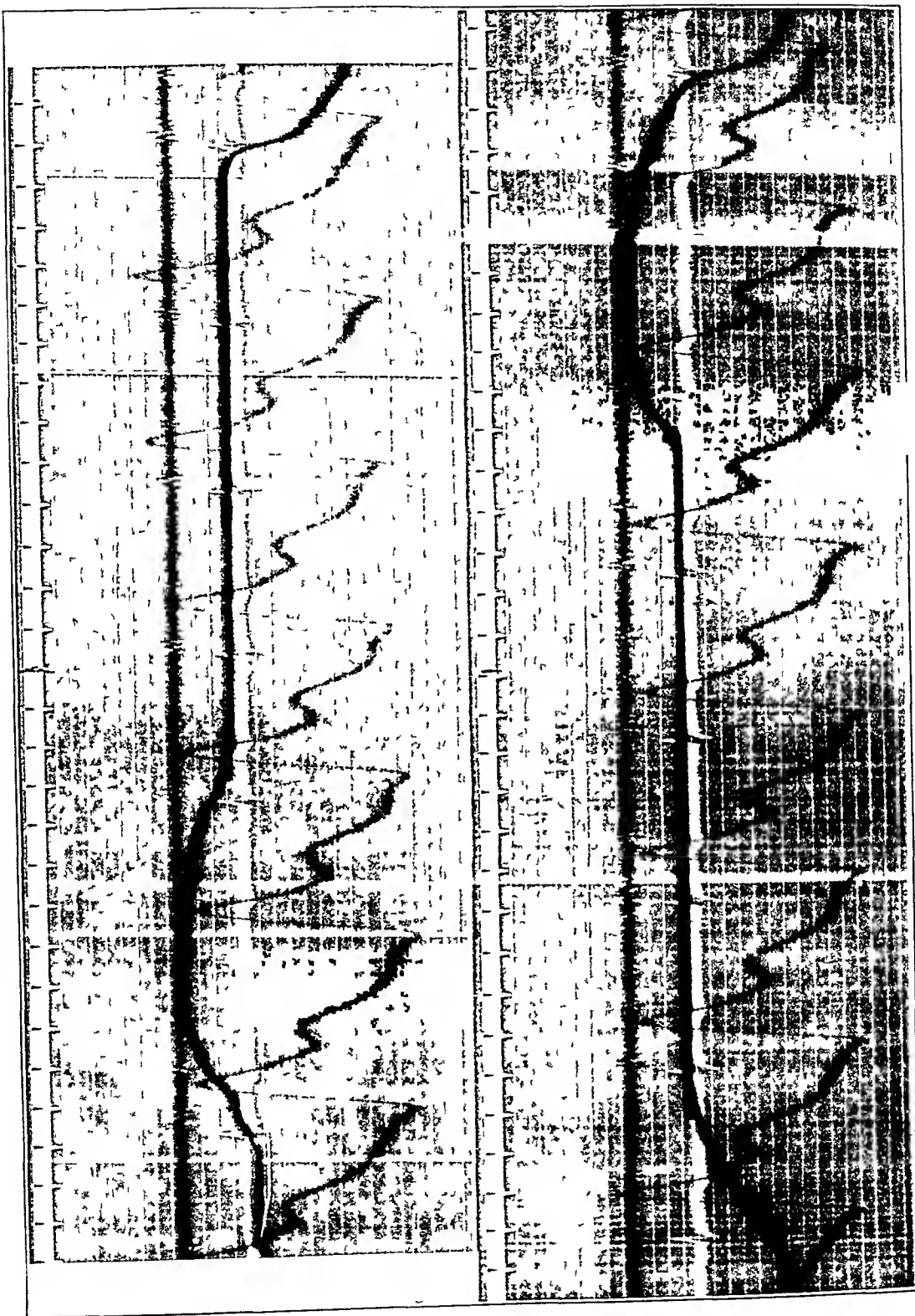


Fig 3.—Pneumotachogram of a normal subject during forced inspiratory and expiratory standstill, with simultaneously registered heart sounds, electrocardiogram and velocity curves of the pulse. The upper and lower tracings form a continuous record

disorders of the lungs, ten cases. The majority of the patients observed had respiratory curves which were identical with those of normal subjects. The pneumotachograph of patients with circulatory failure, as expected, showed an increased respiratory rate, and occasionally increased minute volume. Similarly, the tracings of the majority of the patients gave a straight line during the respiratory standstill. In six patients, however, with aneurysm of the thoracic portion of the aorta, notchlike elevations synchronous with the heart action were observed during both the inspiratory and the expiratory standstill, although the notchlike elevations were more marked in inspiration. An analysis of the notching in its relation to the heart sounds indicated that with cardiac systole a small amount of air is expelled from the lungs, synchronously with the second sound, which corresponds to the closure of the aortic valves, a small amount of air flows back into the lungs although the respiratory muscles are not active.

The phenomena observed, in our opinion, are best explained by recalling that thoracic aneurysms of the aorta are usually in close contact with the pleural surface. Firm adhesions between the wall of the aneurysm and pleura are often observed. The aneurysmal sac of the aorta, therefore, may act as a pressure and suction pump and may produce fluctuations in the content of air in the lungs, which is registered with the sensitive apparatus applied. We observed, altogether, six patients in whom the diagnosis of syphilitic aneurysm was established by clinical evidence, serologic observations and fluoroscopic and roentgen examinations. If observations on a larger number of patients with aneurysm indicate that this notching of the pneumotachogram is present in a high percentage of such patients, the sign should be considered an important and valuable aid in the diagnosis of aneurysm of the aorta.

Following the observations on patients with aneurysm of the thoracic portion of the aorta, studies were made of the inspiratory mechanism of patients with tumors of the lung and pleura. As is well recognized, the differential diagnosis between aneurysm of the aorta and neoplasms located in the mediastinum is occasionally most difficult and sometimes impossible. All the signs of differential diagnostic importance may be present in both conditions. The roentgen shadow of a solid tumor and of a pulsating aneurysm may be identical. It is true that an irregularly outlined shadow favors the presence of tumor, but multilocular aneurysms are not rare. Under fluoroscopic examination, both tumors of the lungs and those of the pleura may show transmitted pulsations which are synchronous with the heart. A shadow which extends into the lung field favors the diagnosis of tumor of the lung, as it is most frequently associated with bronchial carcinoma. This sign, however, may be absent in the case of malignant tumors, and may

be present as a complication in aneurysm. Aneurysms of the arch of the aorta are especially likely to produce compression of the left bronchus which may result in partial or complete atelectasis of certain areas of the lung. Such a clinical condition may give a roentgen and fluoroscopic picture identical with that of a tumor of the lung. Paresis of the recurrent laryngeal nerve and compression of the vena cava may also occur in both conditions. Similarly, hemoptysis may develop in such conditions. Effusions in the pleural cavity may be present both in patients with tumor of the lung and in patients with aneurysm. The practical significance of this differential diagnostic problem has grown during recent years, as the frequency of primary malignant tumors of the lungs has increased considerably both in America and in Europe during the past few years.

We studied the respiratory mechanism of seven patients in whom the diagnosis of tumor of the lung was established by autopsy or by the appearance of metastasis during life. The respiratory curves of all seven cases observed were identical with those of normal subjects. The characteristic notches seen in the pneumotachograms of patients with aortic aneurysms were not observed. Figure 4 represents the pneumotachogram of a patient with aneurysm and of one with tumor of the lung, verified by postmortem examination.

Considering that aneurysm, like mediastinal tumor and tumor of the lung, is relatively rare, the observations on six patients with aneurysm and on seven patients with tumor of the lung are sufficiently large to attach significance to these observations. The possibility that certain aneurysms may not give the sign, and that some mediastinal tumors may produce notchings of the pneumotachogram during respiratory standstill can be ruled out definitely only after a study of a larger number of cases. Repetition of the observations, therefore, will facilitate settling that aspect of the problem.

In addition to the patients with aneurysm of the thoracic aorta, patients with clinical signs of adhesive pericarditis exhibited notchings synchronous with the heart beat during inspiratory standstill, but, in contrast to the patients with aneurysm, they failed to show notchings during the expiratory standstill. Figure 5 is a tracing obtained on a patient with adhesive pericarditis.

Our interpretation of the pneumotachograms of patients with adhesive pericarditis is as follows. It is recognized that in a number of patients with adhesive pericarditis, firm adhesions are present not only between the visceral and parietal layers of the pericardium (*accretio*), but also between the parietal pericardium and pleura (*concretio*). This latter type of adhesion may be intense enough over the diaphragmatic aspect of the pleura to exert a pull on the diaphragm, which in turn, produces a visible pulsation over its place of attachment. This can be

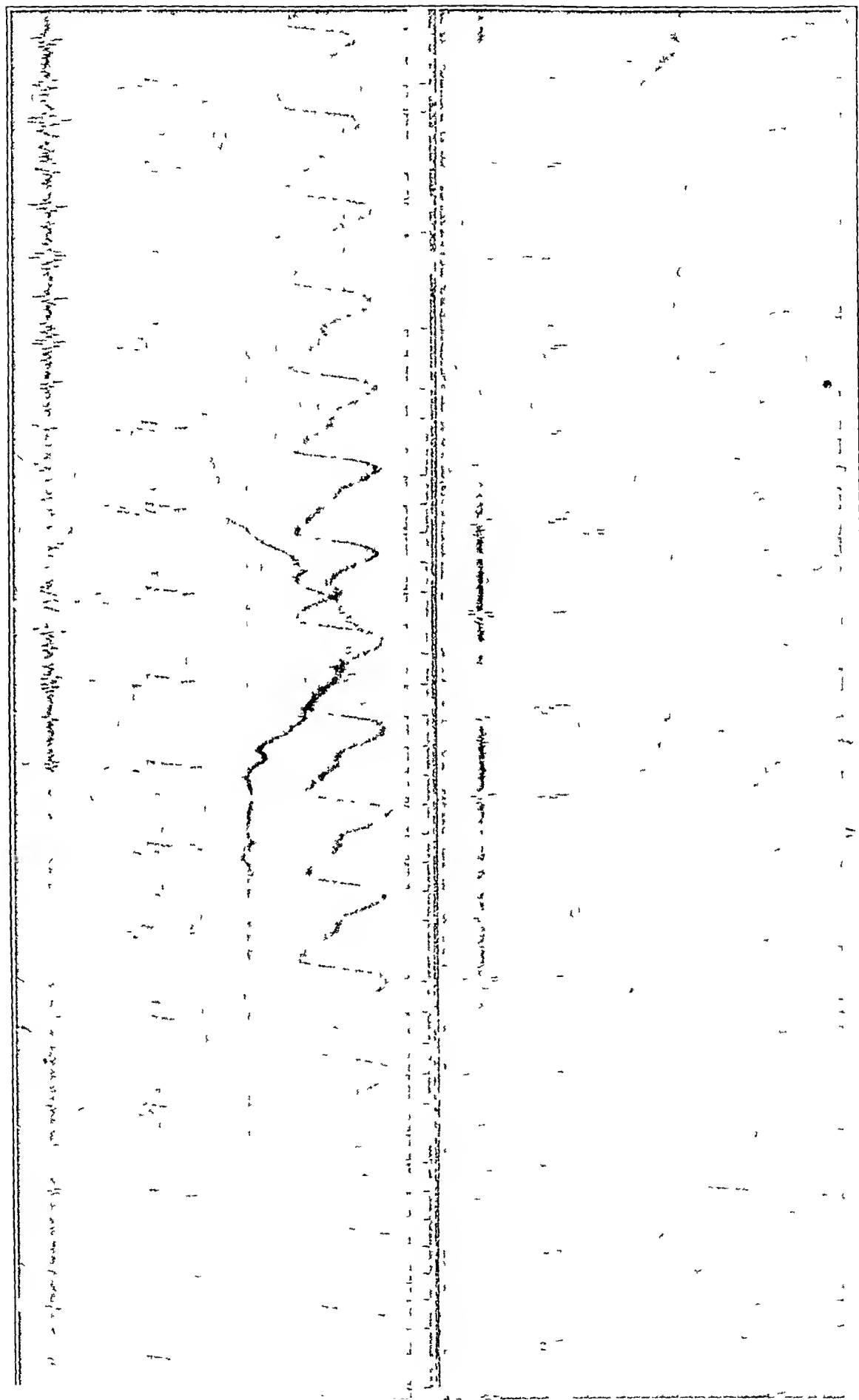


Fig. 4—Pneumotachograms of natural breathing followed by inspiratory standstill in a patient with primary carcinoma of the bronchus of the right lung (upper tracing), and that in a patient with aneurysm of the arch of the aorta (lower tracing)

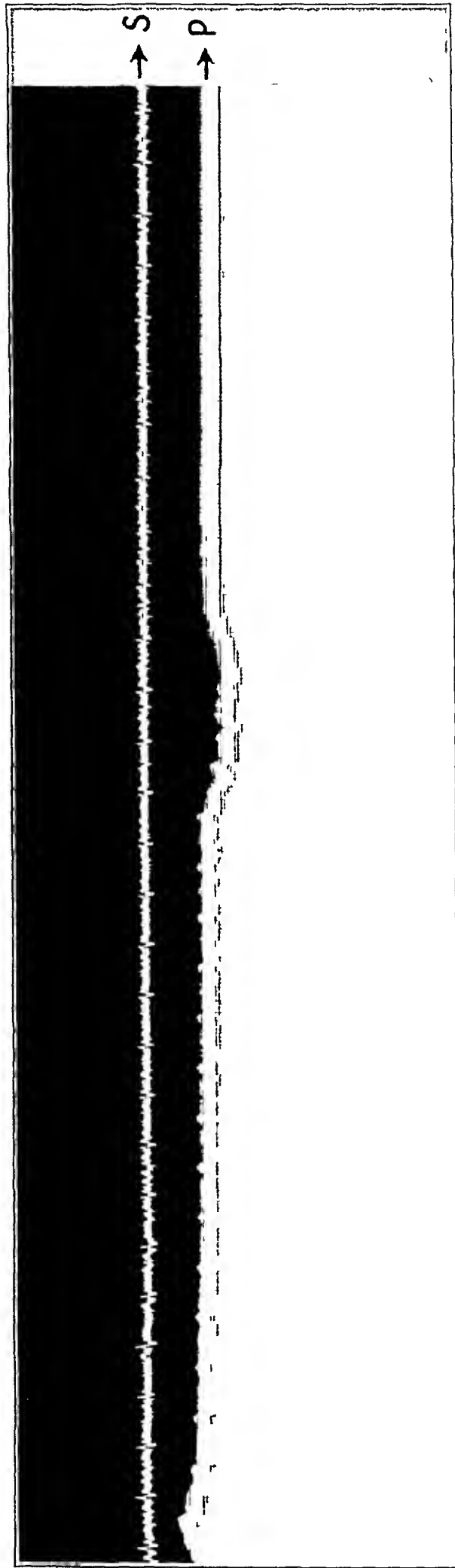


Fig 5—Pneumotachogram of a patient who had chronic rheumatic endocarditis with marked cardiac hypertrophy and Broadbent's sign S is the record of the heart sounds, P is the pneumotachogram during inspiratory and expiratory standstill

observed easily near the region of the floating ribs (Broadbent's sign) This sign is present only in a relatively small percentage of patients with adhesive pericarditis It is our contention that the behavior of the pneumotachogram in adhesive pericarditis depends on identical pathologic changes, with the result that during inspiration when the diaphragm is lowered and the pull of the adhesions is increased, a pulsating movement of the diaphragm will occur which in turn causes a to-and-fro fluctuation of air in the lungs, provided there is a free communication with the outside air During expiration, the adhesions being looser, the pull exerted is insufficient to produce pulsating movements of the diaphragm

Special importance is attached to the fact that in addition to the cases with definite clinical and laboratory observations indicating the presence of adhesive pericarditis, seven of twenty-five patients, or 28 per cent, with chronic rheumatic endocarditis but no signs of adhesive pericarditis showed the same phenomena We believe that the mechanism of the notchings of the respiratory curves in these patients is identical with that observed in patients with clinical manifestations of pericarditis It is recognized that adhesive pericarditis occurs in rheumatic disease of the heart more frequently than one may judge from the clinical behavior of the patients This conception is substantiated by a comparison of the clinical behavior of patients in the Boston City Hospital, who died and in whom the postmortem examination revealed pathologic changes of the mitral aspect of the endocardium characteristic of chronic rheumatic endocarditis An analysis showed that in seventeen of sixty-three cases (27 per cent) of mitral disease, marked adhesions of the pericardium were present although, clinically, in only three instances was adhesive pericarditis suggested

The presence of notchings in the pneumotachograph during inspiratory standstill in a number of patients with chronic rheumatic endocarditis, therefore, may be the only sign indicative of the presence of adhesive pericarditis

#### SUMMARY AND CONCLUSIONS

- 1 The velocity of the respiration during its natural state and during certain respiratory gymnastics was studied in fifty normal subjects and in eighty-three patients with diseases of the heart and lungs

- 2 During inspiratory or expiratory standstill, the pneumotachogram of the normal subjects and of the majority of the patients is a straight line

- 3 In six patients with aneurysm of the thoracic portion of the aorta, notchings of the pneumotachogram were observed during both inspiratory and expiratory standstill

- 4 The pneumotachogram of four patients with clinical evidence of adhesive pericarditis and of seven of twenty-five patients with chronic



rheumatic endocarditis exhibited similar notchings during inspiratory standstill, but the tracing was a straight line during expiratory standstill

5 Registration of the respiration with the pneumotachograph may be of considerable aid in certain diagnostic problems of intrathoracic pathology

6 The observations indicate that under certain pathologic conditions the lungs act as sensitive plethysmographs for recording abnormal changes in the cardiac function

# Book Reviews

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PRAKTISCHE DIFFERENTIALDIAGNOSTIK FÜR AERZTE UND STUDIERENDE VI HAUT- UND GESCHLECHTSKRANKHEITEN I HAUTKRANKHEITEN By PAUL TACHAU, Physician for Skin and Venereal Diseases in Wolfenbüttel-Braunschweig Price, 14 marks Pp 237, with 3 illustrations Dresden Theodor Steinkopff, 1929

This volume is a concise but detailed work dealing with diagnosis and differential diagnosis of dermatoses

Pages 5 to 38 include general considerations of primary and secondary lesions On pages 39 to 142 the monomorphous diseases are considered, and on pages 143 to 197 the polymorphous diseases are dealt with Diseases of the scalp occupy pages 198 to 207, diseases of the nails 207 to 210 and diseases of the mucous membranes 210 to 222

The difficulties in the physical diagnosis of dermatoses make the work of less value to the practitioner who has had no special training in dermatology This defect could have been partially remedied by photographic illustrations of various primary and secondary lesions Since dermatologic diagnosis is governed largely by visual impressions, lack of illustrations is a serious fault The text, however, is valuable in connection with advanced training of persons already founded in fundamental diagnosis

The text is illustrated by three microscopic sketches, although other illustrations are said to form a supplement to the complete volume

An excellent index occupies the last fifteen pages

DIABETES LATENTE By DR FELIX PUCHULU Buenos Aires Ferrari Hnos, 1929

This is the inaugural dissertation of one of the assistants in Escudero's Clinic, and consists of an admirable summary of the work done by the author, his chief and many others on the peculiar manifestations of diabetes in the preglycosuric stage

It is claimed that in normal persons the ingestion of dextrose causes a rise in the blood sugar, followed later by a considerable fall below the point where the test began This secondary fall is caused by the fact that the carbohydrate-storing mechanism has been speeded up Failure of the occurrence of this fall is interpreted as a deficiency in carbohydrate metabolism and is looked on as a precursor of diabetes

Such a condition was discovered in a series of sixty-one persons suffering from skin and ocular diseases of various types When they were subjected to anti-diabetic therapy a marked improvement resulted

THE PRINCIPLES OF CLINICAL PATHOLOGY IN PRACTICE By GEOFFREY BOURNE and KENNETH STONE Price, \$4.75 New York Oxford University Press, 1929

Bourne and Stone's compendium suffers from the same ailment that has afflicted medical books in the past and that will afflict many in the future The ambition of the authors and the range of the subject has impelled a cursory survey of many diseases, the limitation of the size of the book has resulted in a general superficiality As a result, the product is in general unsatisfactory Perhaps a conscious effort to write it down to the supposed level of the practitioner may have something to do with the obviously elementary character Of the 370 odd pages, only 7 are devoted to the stomach, and none of the recent methods of analysis are even mentioned The roentgen rays play no apparent rôle, and of modern chemical analysis of the blood there is hardly a suggestion The book offers nothing of value to the modern practitioner

CARDIAC ARRHYTHMIAS By IRVING R. ROTH Price, \$7.50 Pp. 210 New York Paul B. Hoeber, 1928

The book is written in two sections, the first dealing with the anatomy and physiology of the heart and the second with the cardiac arrhythmias. The reading matter is reduced to a minimum, and diagrams and graphs are used to good advantage in explaining the interrelations of the various clinical phenomena in the normal as well as in the irregular heart beat. The book is especially attractive to the average practitioner and student. It is written clearly and briefly and is illustrated in an enlightening manner.

DAS EXSICCOSERPROBLEM By PROFESSOR DR. ERWIN SCHIFF Price, 6.80 marks Pp. 85 Berlin Julius Springer, 1929

This is an excellent monograph on the subject of water loss by a pioneer worker in this field. Schiff considers the ways in which desiccation of the body is brought about. He discusses the pathologic, chemical and physical changes produced as a result of desiccation. The treatment of desiccation due to various causes is outlined. The bibliography is remarkably complete and includes references to more than 300 articles.

## THE TREATMENT OF PYURIA DUE TO BACILLUS COLI\*

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BOSTON

It is well known that a culture of *Bacillus coli* will become sterile on standing at 37 C, as the colon bacilli are killed by the acid that they themselves produce. Test-tube experiments have shown that the acid culture fluid has a growth-inhibiting, or a deadly, effect on colon bacilli. Thus, a number of authors (Winslow and Lochridge, 1906,<sup>1</sup> Michaelis and Marcora, 1912,<sup>2</sup> Clark, 1915,<sup>3</sup> Dernby, 1921,<sup>4</sup> and Warburg and I, 1925,<sup>5</sup>) have demonstrated that the growth of *B. coli* is inhibited with a hydrogen ion concentration of about  $p_H$  5.

In 1921, Haldane<sup>6</sup> showed that the urine may be acidified to a degree corresponding to about  $p_H$  5 by the oral administration of calcium chloride and ammonium chloride, and in 1924-1925, Warburg and I used this method on patients with infections of the urinary tract as a therapeutic measure against these lesions. In some cases this treatment was augmented by the additional administration of methenamine, as this substance proved particularly effective in acid fluid. The results, published in *Acta medica Scandinavica*<sup>7</sup> showed recovery in about 50 per cent of the cases. At about the same time, Beckmann and van der Reis<sup>7</sup> obtained concordant results with a similar therapy.

As it was evident from these investigations that the disinfecting action of methenamine in infections of the urinary tract is dependent on the acidity of the urine, I thought that it would also be of interest to find out whether some similar condition applies to phenyl salicylate, which has been used for a great many years as a urinary disinfectant.

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\* Submitted for publication, Dec 29, 1928.

From Medical Department B, Bispebjerg Hospital, Copenhagen. Physician in chief, E. Meulengracht.

1 Winslow and Lochridge. *J. Infect. Dis.* **3**: 547, 1906.

2 Michaelis and Marcora. *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **14**: 170, 1912.

3 Clark, W. M., and Lubs, H. A. *J. Biol. Chem.* **30**: 209, 1917.

4 Dernby, K. G. *Ann. d. l'Inst. Pasteur* **35**: 277, 1921.

5 Johansen, A. Hecht, and Warburg, E. *Hospitaltid.* **68**: 745, 1925.

6 Haldane, I. B. S., Hill, R., and Luck. *J. Physiol.* **57**: 301, 1923.

7 Beckmann, K., and van der Reis. *Ztschr. f. klin. Med.* **101**: 229, 1925.

As is well known, phenyl salicylate is a compound of salicylic acid and phenol that passes through the stomach without undergoing any change, in the intestines it is split into its components, both of which are rapidly absorbed and leave the organism by way of the urine, as phenol—the disinfecting part of phenyl salicylate—is combined with sulphuric acid and glycuronic acid

While the urine is still in the bladder, fermentative processes may cause a splitting of this last compound, whereby phenols are set free once more, and it is the oxidation of these phenols that gives the urine its eventual “phenyl salicylate-coloring”

As a rule, phenyl salicylate is given in doses of from 2 to 5 Gm daily, usually together with some acid potion—for instance, *Mixtura acidı sulfurici*,<sup>8</sup> which contains 0.25 per cent sulphuric acid. If the idea here is to acidify the urine in order to further the effect of phenyl salicylate, the usual 3 or 4 tablespoonfuls of the “acid mixture” in twenty-four hours is too small a dose, as Warburg and I have mentioned,<sup>5</sup> for 3 times 15 cc of “acid mixture” contains about 20 cc of tenth-normal mineral acid, while 3 times 1 Gm of calcium chloride corresponds to 75 cc of tenth-normal mineral acid

The use of phenyl salicylate is usually discontinued when the urine becomes phenyl salicylate-colored, for fear of toxic effects from the phenol. The clinicians who have used phenyl salicylate have noticed that, all other factors being equal, some patients show phenyl salicylate-colored urine more rapidly and more readily than do others for no demonstrable reason and, what is more important, without any indication of increase in disinfecting effect concurrent with the phenyl salicylate color

In spite of the phenyl salicylate-colored urine, however, administration of phenyl salicylate has been continued for weeks without causing the patient to give any sign of toxic phenomena

Briefly, such are the guiding principles of phenyl salicylate therapy

My aim in this investigation has been the attempt at forming some idea—partly from my own experiments, partly on the basis of clinical observations—as to the extent to which the disinfecting effect of phenyl salicylate against *B. coli* is dependent on the reaction of the urine

I have not taken up the chemico-analytic aspect of the problem, with its qualitative and quantitative determination of the split products that may be formed in the urine and eventually be active in the various phases of the phenyl salicylate treatment. On the other hand I have tried to

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	Cc
8 R. <i>Acidı sulfurici dilute</i>	20
<i>Syrupı rubı idaei</i>	180
<i>Aqua destillatae</i>	800
	<hr/>
	1,000

find out whether it is practicable during phenyl salicylate treatment to demonstrate any differences in the disinfecting action of the urine against *B coli* on different experimental conditions

### TECHNIC

Briefly, the technic is as follows

Sterile urine is obtained from a patient whose urinary tract is healthy. The specimen is divided into four or five portions, to which hydrochloric acid and sodium hydroxide are added in such amounts as to give a series of differing specimens with  $p_H$  ranging, for instance, from 6.6 to 4.8, with suitable intervals.

I have chosen the zone from  $p_H$  6.6 to 4.8, as it is within this interval that one may alter  $p_H$  of the urine by means of medicamentation—with calcium chloride, for instance.

Under sterile precautions, equal amounts (5 cc, for instance) are pipetted from the various portions of urine of different hydrogen ion concentration (for instance, with  $p_H$  6.4, 5.7, 5.3 and 5) into sterile test tubes. In addition, one should have on hand a number of tubes containing sterile broth.

TABLE 1—Data Obtained in a Series of Transplants (No Medicamentation) \*

$p_H$	First Inoculation, Urine	1 Transplant (4 Hours)		2 Transplant (8 Hours)		3 Transplant (12 Hours)		4 Transplant (20 Hours)	
		Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
7.0	++	++	++	++	++	++	++	++	++
6.2	++	++	++	++	++	++	++	++	++
5.2	++	—	++	—	++	—	++	—	++
4.5	—	—	++	—	++	—	++	—	—
Transplants into Ordinary Broth from Tubes with No Visible Growth									
7.0									
6.2									
5.2				++		++		++	
4.5				++		—		—	

\* In this table and in tables 2, 3, 4, 5, 6, 7, 8, 9 and 10, + indicates visible growth, (++) indicates a considerable inhibition of growth, and —, no visible growth.

Now, transplants are made from a culture of an actively growing, pathogenic strain of *B coli* into two tubes of each kind of specimen of urine of different acidity, and the tubes are left in the incubator for four hours, then transplants are made from each of these tubes into tubes containing urine of the same  $p_H$  as well as into tubes containing ordinary broth. All these transplants are placed in the incubator, and four hours later, new transplants are made from the last ones in the same manner, etc.

The data obtained in such a series of transplants are given in table 1. The results of the transplantations are read after twenty-four hours. From all tubes not showing visible growth, fresh transplants are made into tubes containing broth in order to find out whether the lack of visible growth is due to inhibition of growth or to killing of the bacilli.

The transplants were made every four hours to imitate, as far as possible, the conditions in the organism, when one assumes the bladder to empty itself every four hours. These four hours then leave time for the bacilli to grow as well as time for the eventual bactericidal substances in the urine to counteract the bacterial growth.

I then gave phenyl salicylate, 1 Gm four times daily, to the same patient for four days and repeated the previously described culture experiments with the same colon strain on portions of the same sterile urine, differing in degree of acidity, and with the same transplants, the same time intervals, etc., as in the foregoing experiment. The results of these experiments are given in table 2.

A third series of experiments was carried out with the same patient. This time the same oblique line—from the bottom at the left and upward to the right—just as it does in table 1, consequently, the more acid the urine, the fewer transplants are required for sterility.

A third series of experiments were carried out with the same patient. This time he was given calcium chloride for several days, until the urine gave an acid reaction to methyl red, this reaction was kept up, while the patient received phenyl salicylate, 1 Gm four times daily for four days. The same experiments

TABLE 2—Data Obtained in a Series of Transplants After the Administration of Phenyl Salicylate

$pH$	First Inoculation, Urine	1 Transplant (4 Hours)		2 Transplant (8 Hours)		3 Transplant (12 Hours)		4 Transplant (20 Hours)	
		Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
6.2	++	++	++	++	++	++	++	—	++
5.7	++	—	++	—	++	—	++	—	++
5.3	+(+)	—	++	—	++	—	++	—	++
5.0	—	—	+(+)	—	(+)(+)	—	(+)(+)	—	(+)(+)
Transplants into Ordinary Broth from Tubes with No Visible Growth									
6.2								++	
5.7		++		++		++		—	
5.3	++	++		—		—		—	
5.0	+-	—		—		—		—	

TABLE 3—Data Obtained in a Series of Transplants After the Administration of Calcium Chloride and Phenyl Salicylate

$pH$	First Inoculation, Urine	1 Transplant (4 Hours)		2 Transplant (8 Hours)		3 Transplant (12 Hours)		4 Transplant (20 Hours)	
		Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
6.3	++	—	++	—	++	—	—	—	—
5.7	—	—	++	—	++	—	—	—	—
5.3	—	—	++	—	—	—	—	—	—
4.9	—	—	++	—	—	—	—	—	—
Transplants into Ordinary Broth from Tubes with No Visible Growth									
6.3	++	(+)(+)		++		—		—	
5.7	++	—		—		—		—	
5.3	—	—		—		—		—	
4.9	—	—		—		—		—	

as before were repeated in an analogous manner. The results are given in table 3.

This table shows the same acclivity for the transition from + to — growth, but, as will be noticed, the line has shifted definitely upward to the left, which indicates that the urine has a more disinfecting effect in the last experiment.

This fact is still more obvious when the points at which sterility is ascertained are marked on a coordinate system with the  $pH$  values along the abscissa and the number of transplants along the ordinate. The outcome will be two curves of different courses—one curve for the experiment in which the patient was given phenyl salicylate alone, and a different curve for the experiment in which the patient's urine is acidified, previous to the ingestion of phenyl salicylate, by means of calcium chloride (chart 1). The greater disinfectant power of the urine in the last case is manifest in the smaller number of transplants as well as in its germicidal action in spite of the higher  $pH$  values.

I have repeated these experiments in the same manner with two more patients with healthy urinary tracts and with two other pathogenic strains of *B. coli*, the results obtained were similar to those of the experimental series just mentioned, although to a less pronounced degree. They are given in tables 4, 5 and 6 with the corresponding chart 2, and in tables 7, 8 and 9 with the corresponding chart 3. In charts 2 and 3, the degrees of acidity and the numbers of transplants

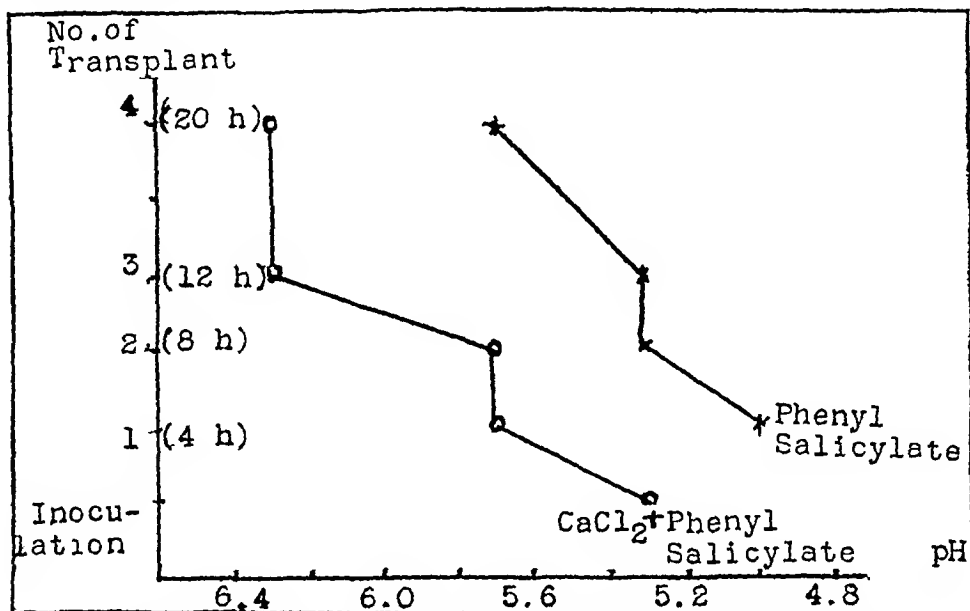


Chart 1—Curves representing the results in tables 2 and 3

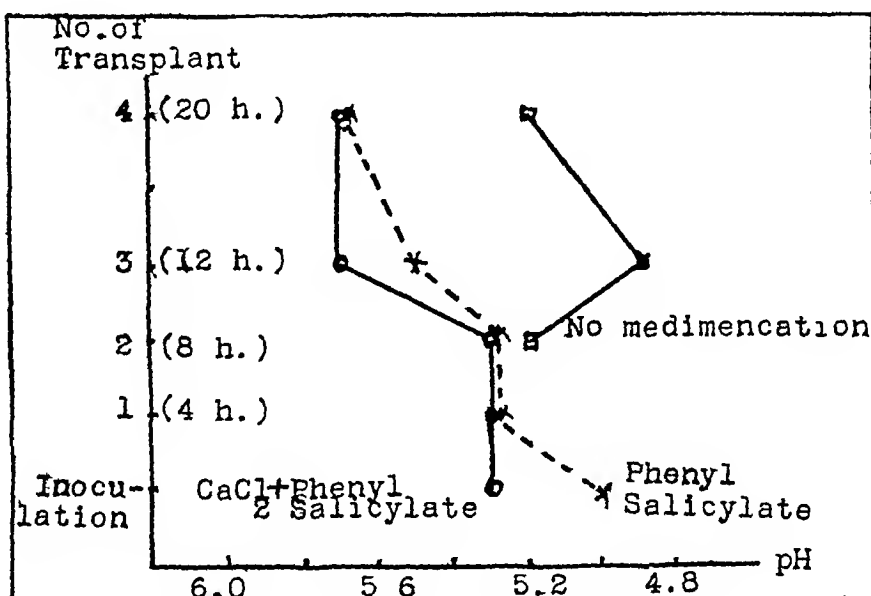


Chart 2—Curves representing the results in tables 4, 5 and 6

at which sterility first appeared are recorded in the same manner as was done in chart 1.

Obviously, the colon strains that are used in the last two series of experiments show a lesser degree of difference in sensitivity when the experiments are made, respectively, with ordinary urine, with urine containing phenyl salicylate and with urine that is kept acid during the phenyl salicylate treatment. I cannot say



whether one might be able to make the difference more conspicuous by carrying out the experiments with a series of urines of differing acidities, in which the difference in  $p_H$  is smaller than that in these experiments

TABLE 4—Data Obtained in a Series of Transplants (No Medicamentation)

$p_H$	First Inoculation, Urine	1 Transplant (4 Hours)		2 Transplant (8 Hours)		3 Transplant (12 Hours)		4 Transplant (20 Hours)	
		Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
64	++	++	++	++	++	++	++	++	++
56	++	—	++	—	++	—	—	—	—
52	—	—	++	—	+	—	—	—	—
49	—	—	++	—	—	—	—	—	—
Transplants into Ordinary Broth from Tubes with No Visible Growth									
64									
56	++	++		++		++		++	
52		++		—		(+)(+)		—	
49		(+)(+)		—		—		—	

TABLE 5—Data Obtained in a Series of Transplants After Administration of Phenyl Salicylate

$p_H$	First Inoculation, Urine	1 Transplant (4 Hours)		2 Transplant (8 Hours)		3 Transplant (12 Hours)		4 Transplant (20 Hours)	
		Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
62	++	++	++	++	++	++	++	++	++
57	++	++	++	—	++	—	++	—	++
53	—	—	++	—	++	—	—	—	—
50	—	—	++	—	—	—	—	—	—
Transplants into Ordinary Broth from Tubes with No Visible Growth									
62									
57	++	++		++		+		—	
53	—	—		—		—		—	
50	—	—		—		—		—	

TABLE 6—Data Obtained in a Series of Transplants After Administration of Calcium Chloride and Phenyl Salicylate

$p_H$	First Inoculation, Urine	1 Transplant (4 Hours)		2 Transplant (8 Hours)		3 Transplant (12 Hours)		4 Transplant (20 Hours)	
		Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
65	++	++	++	++	++	++	++	++	++
56	++	++	++	++	++	++	++	++	++
53	—	—	++	—	++	—	—	—	—
49	—	—	++	—	—	—	—	—	—
Transplants into Ordinary Broth from Tubes with No Visible Growth									
65									
56	++	++		++		—		—	
53	—	—		—		—		—	
49	—	—		—		—		—	

TABLE 7—Data Obtained in a Series of Transplants (No Medicamentation)

$p_H$	First Inoculation, Urine	1 Transplant (4 Hours)		2 Transplant (8 Hours)		3 Transplant (12 Hours)		4 Transplant (20 Hours)	
		Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
60	++	++	++	++	++	++	++	(+)(+)	++
55	++	++	++	++	++	—	—	—	—
52	++	++	++	—	++	—	—	—	—
49	++	—	++	—	+	—	—	—	—
Transplants into Ordinary Broth from Tubes with No Visible Growth									
60									
55									
52				—		—		—	
49		—		—		—		—	

TABLE 8—Data Obtained in a Series of Transplants After Administration of Phenyl Salicylate

pH	First Inoculation, Urine	1 Transplant (4 Hours)		2 Transplant (8 Hours)		3 Transplant (12 Hours)		4 Transplant (20 Hours)	
		Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
62	++	++	++	++	++	++	++	++	++
56	++	---	++	---	++	---	---	---	---
53	---	---	++	---	---	---	---	---	---
49	---	---	++	---	---	---	---	---	---
Transplants into Ordinary Broth from Tubes with No Visible Growth									
62									
56		---		---		---		---	
53	++	---		---		---		---	
49	++	---		---		---		---	

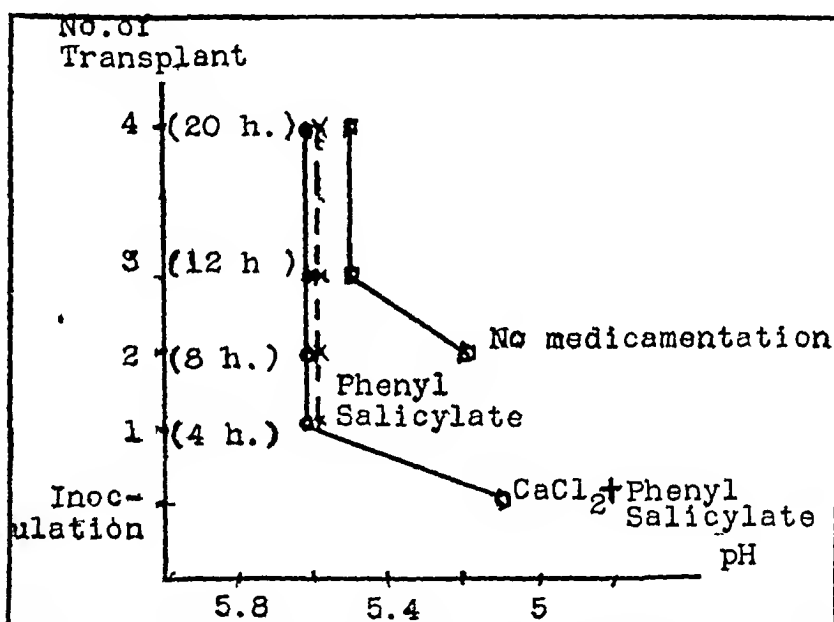


Chart 3—Curves representing the results in tables 7, 8 and 9

TABLE 9—Data Obtained in a Series of Transplants After Administration of Calcium Chloride and Phenyl Salicylate

pH	First Inoculation, Urine	1 Transplant (4 Hours)		2 Transplant (8 Hours)		3 Transplant (12 Hours)		4 Transplant (20 Hours)	
		Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
62	++	++	++	++	++	++	++	++	++
56	---	---	++	---	++	---	---	---	---
53	---	---	++	---	—(+)	---	---	---	---
49	---	---	++	---	---	---	---	---	---
Transplants into Ordinary Broth from Tubes with No Visible Growth									
62									
56	++	---		---		---		---	
53	++	---		---		---		---	
49	---	---		---		---		---	

TABLE 10—*Calcium Chloride and Phenyl Salicylate Treatment in Pyuria Due to B. Coli*

Name	Age	Admission Discharge	Anamnesis	Microscopic Examination of Urine	Bacterial Culture	Daily Dose	No Abnormality on Microscopic Examination of Urine, Days	Urine Sterile, Days	Comment Complications
D M I D	57	Oct 1 Oct 21	Typical symptoms of pyelitis	Leukocytes Bacteria	B coli	Calcium chloride, 6 Gm Phenyl salicylate, 4 Gm	14	11	
I N	63	Oct 29 Nov 22	Typical symptoms of pyelitis	Leukocytes Bacteria	B coli	Calcium chloride, 5 Gm Phenyl salicylate, 4 Gm	8	12	Diabetes mellitus
H A K J	28	Nov 2 Dec 13	Frequent attacks of pyelitis for last six years	Leukocytes Erythrocytes	B coli	Calcium chloride, 8 Gm Phenyl salicylate, 4 Gm	11	20	Parametritis
I N H	23	Dec 9 Dec 13	Typical symptoms of pyelitis	Leukocytes Erythrocytes	B coli	Calcium chloride, 5 Gm Phenyl salicylate, 4 Gm	18	18	
I H	9	Dec 2 Dec 25	Typical symptoms of pyelitis	Leukocytes Bacteria	B coli	Calcium chloride, 3 Gm Phenyl salicylate, 2 Gm	18	18	Pains in stomach after ad- ministration of calcium chloride
K O	74	Nov 24 Dec 30	Painful micturition	Leukocytes Bacteria	B coli	Calcium chloride, 5 Gm Phenyl salicylate, 1 Gm	16	23	Chronic polyarthritis
I S	9	Dec 14 Jan 3	Typical symptoms of pyelitis	Leukocytes Crystals	B coli	Calcium chloride, 3 Gm Phenyl salicylate, 2 Gm	16	16	
I N	34	Dec 4 Dec 29	Tenesmus of bladder, turbid urine	Leukocytes Crystals	B coli	Calcium chloride, 6 Gm Phenyl salicylate, 3 Gm	19	19	
I P	19	Jan 13 Feb 4	Typical symptoms of pyelitis	Leukocytes Epithelial cells	B coli	Calcium chloride, 6 Gm Phenyl salicylate, 4 Gm	?	?	Pregnancy, symptom free discharged on own request
A G L	3	Nov 26 Jan 22	Typical symptoms of pyelitis	Leukocytes Bacteria	B coli	Calcium chloride, 2 Gm Phenyl salicylate, 1 Gm	14	?	Symptom free, but ---+ growth
I N M N	10	May 24 June 15	Pyelitis five times since 1925	Leukocytes Rods	B coli	Calcium chloride, 6 Gm Phenyl salicylate, 2 Gm	18	19	

K P	10	April 8 May 1	Pyelitis seven years ago, symptoms again	Sediment Rods	B coli	Calcium chloride, 3 Gm Phenyl salicylate, 2 Gm	17	17
M B	35	Feb 12 Mar 3	Typical symptoms of pyelitis	Leukocytes	B coli	Calcium chloride, 4 Gm Phenyl salicylate 4 Gm	10	10
M J	68	April 24 May 26	Cystitis three years ago, symptoms again	Leukocytes Epithelial cells	B coli	Calcium chloride, 5 Gm Phenyl salicylate, 4 Gm	?	?
B I N	69	April 20 May 25	Cystitis two times before, symptoms again	Leukocytes Rods	B coli	Calcium chloride, 4 Gm Phenyl salicylate, 4 Gm	?	?
J H	26	June 15 July 2	Persistent cystitis for two years, in spite of treatment	Leukocytes Epithelial cells Rods	B coli	Calcium chloride, 5 Gm Phenyl salicylate, 4 Gm Later, 3 tablets three times daily *	9	9
I P	28	June 6	Dyspepsia for last three years, pains in left side	Leukocytes Epithelial cells	B coli	Three tablets three times daily	10	10
A F	30	June 18 July 13	Attacks of ureteral colic for last three years	Leukocytes Epithelial cells	B coli	Three tablets three times daily to three tablets four times daily Three tablets three times daily	18	13
K L	26	April 16	Periodic pyelitis for several years	Leukocytes Epithelial cells	B coli	Three tablets three times daily	7 (+ few leukocytes)	8
A C	41	May 12 June 25	Painful urination for several years	Leukocytes Rods	B coli	Three tablets three times daily	?	12
I	53	June 27 July 18	Various, indefinite pains, no pains on urination	Leukocytes Rods	B coli	Three tablets three times daily	15	7
L O	30	July 5 July 24	Persistent pyelitis postpartum, June 19	Leukocytes Rods	B coli	Three tablets three times daily	10	10
K H	72	June 25 Aug 8	Uremia on admission	Leukocytes Erythrocytes	B coli	Three tablets three times daily	?	10
J H M	71	June 17 July 3	Chronic cystitis for many years, heart disease, pulmonary tuberculosis	Leukocytes Rods	B coli	Three tablets three times daily	?	?

\* The tablets consisted of calcium chloride coated with phenyl salicylate

No growth, no tubercle bacilli, leukocytes, +, erythrocytes, +  
No effect from tablets, discharged after twenty two days on own request

In chart 3, it is shown that the effect of phenyl salicylate and that of calcium chloride and phenyl salicylate are mostly parallel, but on one single point the latter method excels. Chart 2 and, at any rate, chart 1 show a more conspicuous difference in the disinfecting power of the urine on the different experimental conditions.

#### COMMENT

From these experiments it seems evident that, whatever the underlying process may be, the urine gains in disinfecting power when it is kept acid during the treatment with phenyl salicylate. It is possible that some cleavages take place, with splitting of the phenol that is bound to the acids. It cannot be the effect of the acidity itself on the bacteria that sustains the bactericidal effect in the third section of the experimental series, this much is evident from the arrangement of the experiments, as  $p_H$  is made to vary to the same extent in all three sections (of the experiments) within each series by the addition of acid or base. And yet, the last section of each series shows a greater disinfectant effect than do the other sections of the respective series, in spite of the same  $p_H$  values throughout each series. Some process, then, must have taken place within the organism whereby the disinfecting power of phenyl salicylate is further intensified when the urine is kept acid during the treatment with phenyl salicylate.

This fact, that the disinfecting power of phenyl salicylate is increased by concurrent acidification of the urine, is perhaps something that has been surmised for some time. But, as far as I know, no therapy with phenyl salicylate has previously been instituted against pyuria caused by colon bacilli in which suitable acidity of the urine was made sure of beforehand. These experiments, then, encouraged me to try out a therapy on this basis in patients with pyuria due to *B. coli*.

So I gave the patients calcium chloride—usually 1 Gm—five times daily till the urine proved acid on a qualitative test with methyl red. The test consists simply in adding two or three drops of a 1 per cent solution of methyl red to about 10 cc of urine. If the urine takes on a red color, then it has reached a suitable degree of acidity ( $p_H$  less than 5.5), if, on the other hand, the urine remains yellow, it is necessary to increase the dose of calcium chloride until the urine is colored red by the indicator.

I have taken care to keep the urine at this degree of acidity by suitable dosage of calcium chloride, while at the same time I have given the patients 1 Gm of phenyl salicylate four times a day, I have continued this treatment until the catheterized urine proved sterile on culture, which test was made every week.

The results in the patients whom I have treated in this manner are given in table 10 in such a way as to furnish a quick survey of the course of the treatment. In order to avoid the repetitions in giving the details of the various ordinary case histories, I have given only the chief features of each case.

As shown in table 10, the last nine patients received slightly different treatment

As it was found that the calcium chloride tablets cause cardialgia in some patients and dyspeptic symptoms in others, I thought about the possibility of avoiding this drawback by coating the tablets with phenyl salicylate, so that the calcium chloride would pass through the stomach without undergoing any change

Considering that phenyl salicylate and calcium chloride are used in somewhat constant proportions in this method of treatment, I communicated with a pharmaceutical firm (Medicinalco, Ltd, Copenhagen) in regard to the possibility of preparing tablets of 0.6 Gm calcium chloride with a coating of about 0.3 Gm of phenyl salicylate. After some experimentation, the manufacturers succeeded in producing such tablets. I have treated a number of patients with these tablets, using 3 three times daily for standard doses. Within a few days, the urine would give an acid reaction toward methyl red, just as it did in the earlier treatment with calcium chloride and phenyl salicylate, in a single instance the urine was phenyl salicylate-colored. Dyspeptic conditions developed in no instance, not even on ingestion of 15 tablets a day. One of the patients suffered from dyspepsia beforehand, and his condition was not aggravated during the treatment.

Thus the same effect was attained with these tablets as when calcium chloride and phenyl salicylate were given separately, by this treatment, dyspepsia was avoided altogether. The treatment with pyelol tablets is therefore easy to carry through, it is innoxious, and it can eventually be given as ambulatory treatment. In most of the cases in which it was employed,<sup>9</sup> this treatment resulted in recovery.

#### SUMMARY

It is shown experimentally that the disinfecting power of phenyl salicylate against *B coli* is increased by concurrent acidification of the urine.

When calcium chloride and phenyl salicylate were employed together in the clinical treatment of twenty-four patients suffering from pyuria, cures were obtained in 75 per cent.

Calcium chloride alone caused the development of gastric symptoms in some patients, but this was avoided by giving the calcium chloride in tablets coated with phenyl salicylate which contained the proper proportions of both phenyl salicylate and calcium chloride.

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9 As these tablets, on account of the coating of phenyl salicylate, pass through the stomach without any discomfort, they are particularly serviceable also in such lesions as bronchial asthma, tetany, urticaria and other conditions with itch of the skin in which one would be inclined to institute a treatment with calcium chloride but forbears to do so on account of dyspeptic troubles.

# BENIGN GASTRIC AND DUODENAL ULCERS

CLINICAL DIAGNOSIS AND THE CONDITIONS FOUND AT OPERATION \*

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The more we can learn about peptic ulcer, the more accurate we can be in the recognition of its type, activity and microscopic changes, and the better we understand the complications, the more intelligently we can advise treatment for individual cases.

Surgical treatment for peptic ulcer probably offers the better chance for rapid and permanent cure, particularly in complicated cases, but certain patients respond well to nonsurgical measures and remain entirely without symptoms for an indefinite period. Some patients with peptic ulcers fail to benefit permanently, or perhaps even temporarily, from a medical regimen. In some of these patients the reasons for failure are that the ulcer which is being treated is a penetrating lesion, or perhaps it is one in which obstructive features are easily recognizable. A carefully taken history usually will include information from which fairly accurate deductions regarding the microscopic changes of a lesion can be obtained. Previously it has been pointed out by one of us (Rivers<sup>1</sup>) that patients with ulcer, who have severe epigastric pains, especially if these pains are referred through to the back, or upward into the chest, are likely to do poorly on a nonsurgical regimen. Patients with such symptoms usually have a perforating type of lesion, and as a rule, they come to operation before permanent relief is obtained.

Another pitfall which usually can be avoided by taking a careful history is failure to recognize other pathologic entities which may exist in conjunction with a peptic lesion. It is obvious that the nonsurgical treatment of ulcer, under such circumstances, usually would be a waste of time and a great injustice to the patient. It is common knowledge that peptic ulcer often is found in conjunction with varying degrees of cholecystitis and appendicitis. Although this "trinity of disease" is far from unusual, one or the other pathologic entity is almost certain to demand especial consideration in diagnosis because of the predominant grouping of pertinent symptoms. Peptic ulcer may be present and

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\* From the Division of Medicine, the Mayo Clinic.

1 Rivers, A. B. New Developments in the Treatment of Peptic Ulcer with Notes on the Preoperative Care and Management of Complications, *Journal-Lancet* 48 21, 1928.

there may be definite characteristics in the history suggesting that it is active, yet concurring secondary conditions ultimately may prove of great importance, and the apparently dominating condition may respond differently to therapeutic attempts because of variations in the importance of the secondary condition

Smithies,<sup>2</sup> in reviewing the observations following laparotomy in 264 cases of gastric ulcer, stated "In 35 per cent of instances, diseased appendix was associated with gastric ulcer. In 15 per cent cholecystitis and cholelithiasis were demonstrated as concomitant processes. In view of these figures, it is evident that all laparotomies should be thoroughly explored even when a well marked gastric ulcer has been demonstrated." Smithies also found as associated lesions, Lane's kink twice, carcinoma of the gallbladder once and pancreatitis four times. Eusterman,<sup>3</sup> in reviewing a series of surgically verified gastric and duodenal ulcers, found that associated disease in the appendix occurred in 40 per cent and in the gallbladder in 97 per cent.

#### PURPOSE OF STUDY

In glancing over a large series of histories of cases in which the preoperative diagnosis is gastric or duodenal ulcer, one is impressed with the variety of associated diseases that is found at operation. Many problems immediately present themselves, and about a few of them we decided to gather information with the following purposes in mind: (1) to acquaint ourselves with the diseases that may be hidden in the ulcer syndrome sufficiently to pass unrecognized in the preoperative observation of the clinicians and the consulting surgeons, (2) to determine whether more careful evaluation of symptoms and observations, with probable greater accuracy in detection of associated diseases, would materially benefit the patient, (3) to answer, if possible, the question as to whether the probability of coexisting disease should influence us in advising surgical treatment for a patient with an ulcer which we believe would respond well to a medical regimen, and (4) to focus our attention on the rarer associated diseases, giving brief illustrative case histories to see if by any signs we could have suspected the pathologic changes encountered at operation.

#### MATERIAL

The material for study included the records of 1,075 patients in whom ulcerating lesions of the stomach and duodenum were found at

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2 Smithies, Frank. Gastric Ulcer Without Food Retention. A Clinical Analysis of One Hundred and Forty Operatively Demonstrated Cases, *Am J M Sc* **164** 340, 1913.

3 Eusterman, G. B. The Essential Factors in the Diagnosis of Chronic Gastric and Duodenal Ulcers, *J A M A* **65** 1500 (Oct 30) 1915.



operation A prerequisite to inclusion of these histories in the series was that the diagnosis of a single lesion, such as gastric ulcer or duodenal ulcer, must have been made preoperatively Histories of cases in which a dual diagnosis, such as gastric ulcer and cholecystitis, was made by the clinician were not accepted for study Cases in which another condition was diagnosed that was irrelevant to the condition in the stomach or duodenum, for instance, a case with the diagnosis of duodenal ulcer and hypertrophic arthritis of the right knee, were not excluded from this series The pathologists' reports were taken as the final diagnosis when the tissues were removed In a great number of these cases, however, tissue was not removed, in these, the surgeon's diagnosis was accepted

This series of 1,075 cases included 700 of duodenal ulcer and 375 of gastric ulcer

#### LESIONS FOUND IN PATIENTS OPERATED ON FOR DUODENAL ULCER

Chart 1 is a graphic representation of the various lesions found at operation after a clinical diagnosis of duodenal ulcer had been made The data were compiled from a study of 700 cases In 38 per cent, duodenal ulcer was the sole abnormality found at operation In 62 per cent, some pathologic entity not specified preoperatively was found to be associated with the peptic ulcer The diagnosis of diseased appendix was made by the operating surgeon in 51.8 per cent of the cases, in only 7.4 per cent, however, was the appendix acutely or subacutely inflamed Hence, 14.3 per cent of all cases of appendicitis found in patients operated on for ulcer of the duodenum seems to have been of noteworthy significance In 3.6 per cent of the 700 patients, distinct cholecystitis also was found An associated ulcer in the stomach was noted in 3.6 per cent of the cases from which this chart was compiled A rather curious fact is that this small group included eight cases (1.1 per cent included in the miscellaneous group) in which gastric ulcer was found after the clinician, basing his diagnosis of position of the lesion mainly on the roentgen data, had made a diagnosis of duodenal ulcer There is a miscellaneous group of 3 per cent Among the more unusual observations are duodenitis without actual ulcer, 0.7 per cent, benign tumors 0.4 per cent, Meckel's diverticulum, 0.3 per cent, duodenal diverticulum, 0.14 per cent, and one of carcinoma of the stomach, 0.14 per cent Attention should be called here to the fact that in 700 operations for duodenal ulcer, only once was a carcinoma discovered

#### LESIONS FOUND IN PATIENTS OPERATED ON FOR GASTRIC ULCER

Chart 2 represents graphically the lesions found at operation after a preoperative diagnosis of gastric ulcer had been made It will be

noted that in a little more than half of these patients, 50·8 per cent, a lesion other than the gastric ulcer was not discovered. Associated appendicitis was reported by the surgeon in 38·8 per cent of these cases. Of this group, however, in only 3·1 per cent was the appendix in a state of subacute or acute inflammation. Duodenal ulcer in association with gastric ulcer was found twenty times, or 5·2 per cent. Cholecystitis was found eight times or 2·1 per cent. Probably the most important fact which is apparent from a study of these data is that

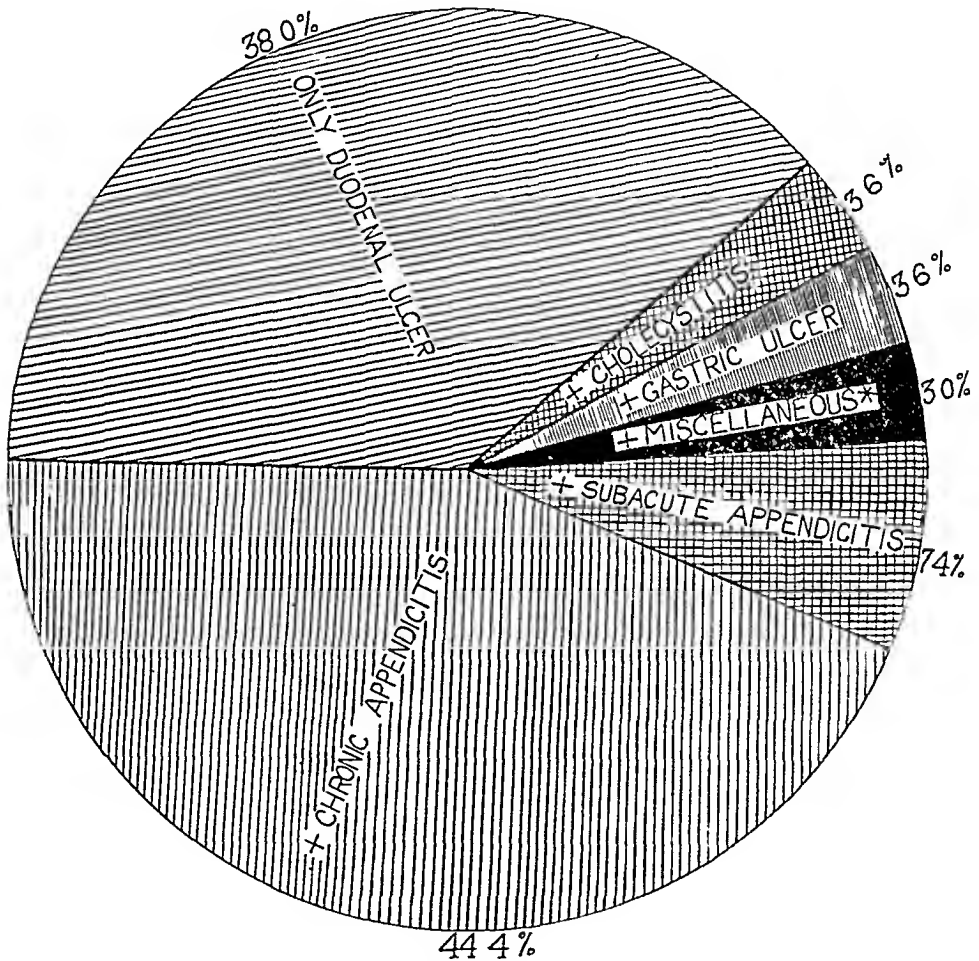


Chart 1—Percentage of lesions found at operation after duodenal ulcer had been diagnosed clinically. In the section designated miscellaneous are included gastric ulcers only, 1·1 per cent, duodenitis only, 0·7 per cent, benign tumors, 0·4 per cent, Meckel's diverticulum, 0·3 per cent, duodenal diverticulum, 0·14 per cent, and associated carcinoma of the stomach, 0·14 per cent.

changes which aroused suspicion of a malignant condition were found in 2·1 per cent of these ulcers. The more unusual lesions discovered in the course of laparotomy on patients included in this group were Lane's kink in 0·26 per cent, calcareous lymph node of the jejunum, in 0·26 per cent, splenitis, in 0·26 per cent, and gastritis without pathologic evidence of gastric ulcer in 0·26 per cent.

LESIONS FOUND IN PATIENTS OPERATED ON FOR EITHER  
DUODENAL OR GASTRIC ULCER

Chart 3 represents a combination of chart 1 and 2. These cases have been subdivided into four groups. The groups will be considered separately.

*Group 1*—This includes (a) cases in which only the gastric or duodenal ulcer preoperatively specified was found, (b) cases in which

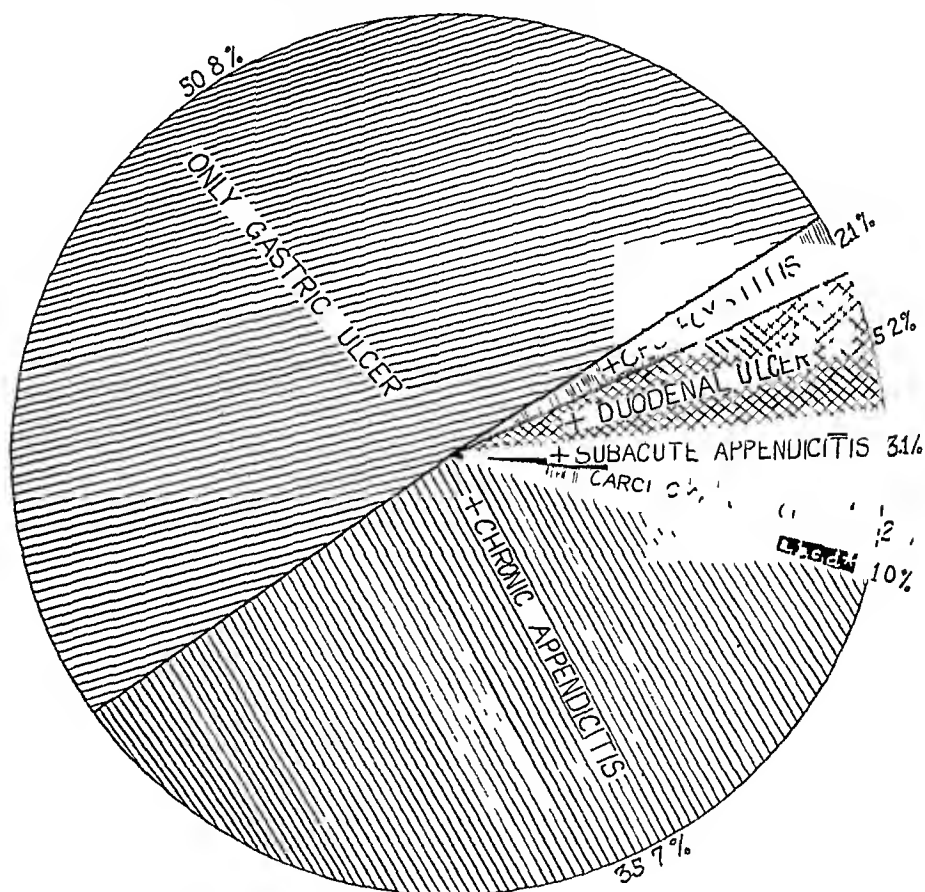


Chart 2—Percentage of lesions found at operation after gastric ulcer had been diagnosed clinically. In the section designated a, b, c, d, are included Lane's link, 0.26 per cent, cancerous gland of the jejunum, 0.26 per cent, gastritis only, 0.26 per cent, and splenitis, 0.26 per cent.

both duodenal and gastric ulcers were found, (c) cases in which, in addition to ulcer, chronic appendicitis was found.

In 42.3 per cent of the total number of cases included in this group, operation revealed only the pathologic condition diagnosed by the clinician. Furthermore, the lesion was found in the location indicated preoperatively. In forty-six instances, or 4.2 per cent, both duodenal and gastric ulcer were discovered at operation. Frequently there were multiple ulcers in the stomach or duodenum. This becomes of some importance when one considers that the surgeon who is satisfied with

only the ulcer which already has been found, and fails to explore further, may overlook secondary ulcers. Thus, a situation may arise which is extremely unpleasant for the patient and embarrassing for the surgeon. In the cases diagnosed as gastric ulcer, combined ulcers were found a little more frequently than in those with the diagnosis of duodenal ulcer. In 36 per cent of the cases diagnosed as duodenal

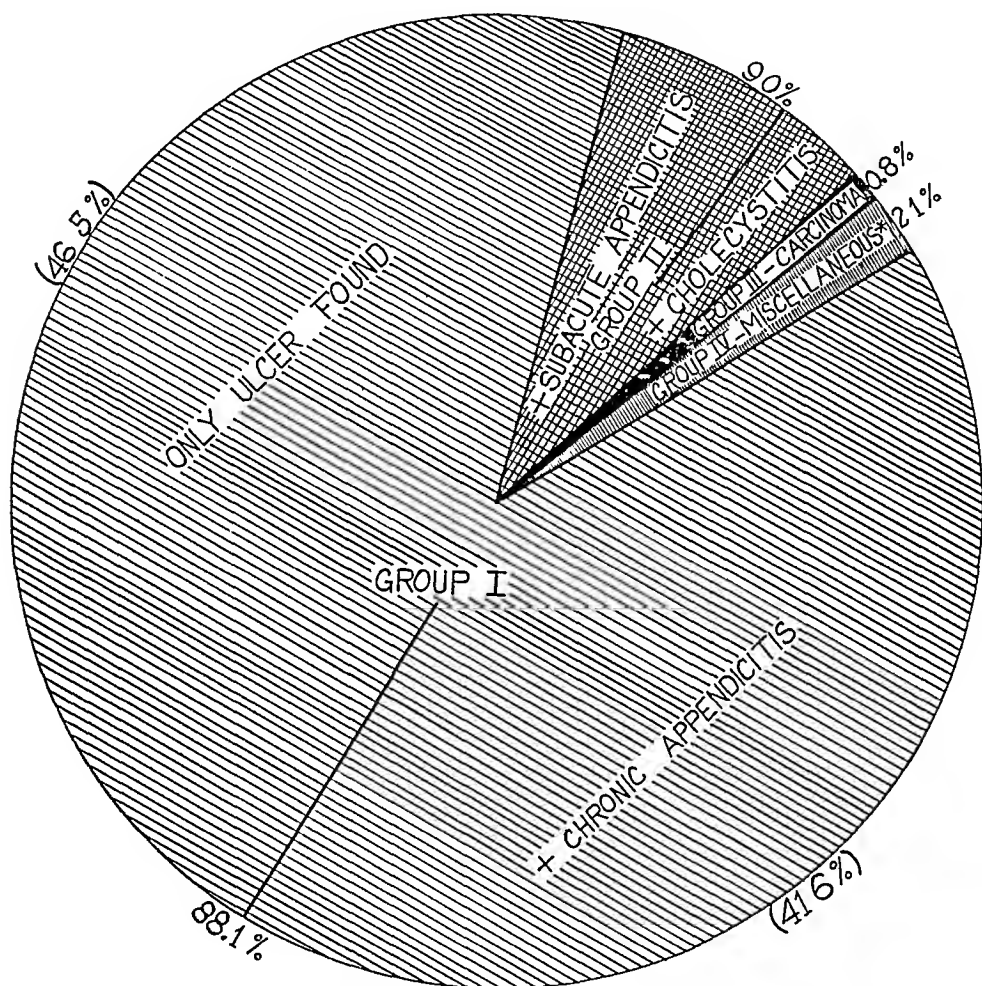


Chart 3—Percentage of lesions found at operation, arranged in groups, after duodenal ulcer and gastric ulcer had been diagnosed clinically. In the section designated miscellaneous are included benign tumors, 0.3 per cent, duodenitis or gastritis, 0.5 per cent, diverticula, 0.3 per cent, Lane's kink, calcareous gland of the jejunum, and splenitis, one case each, 0.3 per cent, and opposite ulcer 0.7 per cent.

ulcer, gastric ulcer also was present, whereas in 52 per cent of those diagnosed as gastric ulcer, combined ulcer was present. The lesion most frequently associated with peptic ulcer is a chronically inflamed appendix. Forty-one and six-tenths per cent of the patients sent to operation with a diagnosis either of gastric or of duodenal ulcer were found to have chronic appendicitis also.

The frequency of appendicitis deserves some comment. At the usual ulcer age there are, as a rule, some chronic inflammatory changes in all appendixes. Carnett<sup>4</sup> expressed the opinion that the appendix in practically every adult shows some evidence of previous inflammation. It is customary at the Mayo Clinic to remove all appendixes whenever practicable during the course of the less complicated laparotomies. This procedure has, of course, certain limitations enforced by age, the general condition of the patient, emergency operation and other conditions. In the ulcer group usually there are no contraindications to secondary operative procedures such as appendectomy. Removal of the appendix does not materially increase the risk of the operation, and such a procedure may save the patient another operation at a later date. The importance of associated appendicitis, however, should not be overestimated. There is some doubt that a mildly inflamed appendix will cause gastro-intestinal symptoms of any great importance. These patients obviously did not make a serious complaint referable to the lower right quadrant, or some suggestion of the possible coexistence of this lesion would have been included in the consulting physician's resume of the case.

The argument advanced by certain surgeons and pathologists for the routine removal of appendixes encountered during laparotomy is that the appendix may become a focus of infection, thus disseminating disease elsewhere through the abdomen. Regarding this, Carnett and Boles<sup>5</sup> have the following to say:

Many of the theories relative to chronic appendicitis causing distant lesions originated before it was realized how commonly the appendix shows gross or microscopic evidence of chronic changes due to normal evolution of the organ. The fairly constant findings of alterations in every appendix removed coincident with operations on the stomach, duodenum or gallbladder are not to be regarded as cause and effect. The same changes are noted in appendixes removed incidental to operation on pus tubes or right inguinal hernias. Aberrant or retrograde lymph flow from a chronically diseased appendix might, therefore, just as logically be ascribed as the cause of pus tubes or right inguinal hernia as of gastric ulcer or biliary disease. There is no doubt that toxins and bacteria carried in the portal circulation may cause pathologic change in the liver or gallbladder, but there is no good reason to believe that these noxious agents originate in a comparatively small sclerosed appendix rather than elsewhere in the large sewage system of the intestinal tract.

*Group 2*—In this group are included cases in which in addition to peptic ulcer, acute or subacute appendicitis or cholecystitis was present.

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4 Carnett, J. B. Chronic Pseudoappendicitis Due to Intercostal Neuralgia, *Am J M Sc* **174** 579, 1927.

5 Carnett, J. B., and Boles, R. S. Fallacies Concerning Chronic Appendicitis, *J A M A* **91** 1679 (Dec 30) 1928.

Acute or subacute appendicitis was found unexpectedly as an associated lesion complicating peptic ulcer sixty-three times, or 59 per cent, in 1,075 operations. This complication, it will be recalled, was discovered in patients operated on for duodenal ulcer in 74 per cent of 700 cases. It is interesting that of the patients on whom operation was performed for gastric ulcer, only 31 per cent were found to have definite inflammation in the appendix. The greater prevalence of this complication in those patients who were operated on for duodenal ulcer probably finds some explanation in the fact that these patients are usually younger, and thus are more likely to be in that period of life when acute appendicitis is most common. That the presence of acute or subacute appendicitis should have remained undetected in these patients is rather strange. Of course, even severe appendicitis may give few, if any, symptoms, and may even go on to rupture without causing much pain. There is the possibility, also, that patients who are having enough distress from peptic ulcer to cause them to undergo operation might ignore the presence of less severe pain in the lower right quadrant and thus might fail to complain of distress in that area. The pain of appendicitis is not infrequently situated just to the right and but very slightly below the level of the umbilicus. Undoubtedly, therefore, even though the patient might complain of pain in this area it might be assumed that peptic ulcer would explain this also. Our experience leads us to believe that a patient with gastric or duodenal ulcer rarely localizes his pain in an area which could be confused with that of an inflamed appendix. Almost invariably the patients who are found at operation to have an appreciable degree of appendicitis will have an area of definite tenderness easily distinguishable from that usually expected in patients who have ulcer alone. In spite of what can be brought forward in defense of the examining physician who fails to suggest definite disease in the appendix, even in the presence of a known peptic ulcer, there is reason to suspect that he was hasty in his examination of the abdomen or that he was too easily satisfied with the diagnosis of the case when the roentgenologist reported finding deformity in the stomach or duodenum.

Cholecystitis in addition to a gastric or duodenal lesion was discovered at laparotomy in 31 per cent of the cases in which the clinical diagnosis had been either gastric or duodenal ulcer. It will be recalled that when cases in which the diagnosis was gastric ulcer were being considered in a class by themselves, disease of the gallbladder was found in 21 per cent. Similar consideration of the patients on whom operation was performed after a diagnosis of duodenal ulcer was made showed that in 36 per cent the gallbladder was sufficiently diseased to justify its removal. An error of 31 per cent in this group is surprisingly low, particularly when it is considered that the symptoms of

cholecystitis and peptic ulcer may be difficult to differentiate. It is doubtful if, with the help of meticulously taken histories and added experience with cholecystography, we shall be able to improve much on this figure.

*Group 3*—This group includes cases of malignant lesions, and lesions suspected of being malignant which were found in the course of laparotomy performed after a preoperative diagnosis of gastric or duodenal ulcer. Because of the importance of this complication, we are submitting for analysis the individual histories of all of the eleven patients in this group, in all but one, the preoperative diagnosis was gastric ulcer.

In the first two cases, specimens removed were diagnosed microscopically as carcinoma, and this leaves no doubt that the lesions were malignant.

*CASE 1*—A man, aged 62, had had intervals of dyspepsia for twenty-five years. He had suffered from pain in the midepigastrium which had come on two hours after meals. Frequently pain had awakened him at 3 a. m. Sodium bicarbonate had relieved him although for a short time previous to his admission to the clinic, relief had not been complete. He had had daily distress for six months. During this time he had noticed a loss of weight of 6.8 Kg. During the month before admission, he frequently had avoided food for two or three days because then he was more comfortable. He was examined in the clinic. Gastric analysis<sup>6</sup> revealed total acids 60, free hydrochloric 42 and total content recovered 1,000 cc. The report of the roentgenologist was duodenal ulcer with obstruction. After preoperative preparation, operation was performed. On the duodenal side of the pylorus was an ulcer, on the gastric side, a perforating carcinoma.

This is the only case included in our series in which the diagnosis was duodenal ulcer and in which a malignant condition was found at operation. Carcinoma of the duodenum is so rare that its differential diagnosis needs scarcely be considered in dealing with duodenal ulcer. In this instance, the marked obstruction was perfectly evident to the roentgenologist, but the area of malignancy, which was near the pylorus on the gastric side, was not visualized. By general examination, one would have been unable to detect the carcinoma, and there was nothing in the history to suggest such a complication. The history of a disturbance of twenty-five years' duration is characteristic of ulcer. The recent change in symptoms was due to obstructive features being superimposed on those caused by the old ulcer. Either the ulcer or the carcinoma may have caused the obstruction.

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6 In each instance throughout this paper, the quantitative expression of acidity of gastric contents is in terms of number of cubic centimeters of tenth normal solution of sodium hydroxide required to neutralize 100 cc. of gastric contents. The quantity reported as the content recovered is obtained one hour after the test meal has been given.

CASE 2—A woman, aged 51, had had pain in the upper portion of the abdomen for one month. Pain came on about one hour after the meal, and radiated upward into the left side of the chest. There was much gas, belching and regurgitation of acid gastric contents. She vomited at intervals. Distress was worse when the stomach was empty. Occasionally she was awakened at night by pain in the epigastrium. Analysis of gastric contents revealed total acidity ranging from 12 to 24 and persistent achlorhydria, the quantity of content recovered was 247 cc. The report of roentgen examination was that pyloric spasm and a suggestion of a small gastric ulcer were present. At operation, early carcinoma on the border of a gastric ulcer was found.

Roentgen observations in this case did not help much except to localize the lesion. Clinically, however, there was much evidence which might have led one to suspect the presence of a complicated gastric ulcer. The age of the patient, the short history and the persistent anacidity should have made the clinician suspicious of the presence of a malignant ulcer or early carcinoma. A history of the ulcer type is not at all uncommon in a malignant condition. Often these patients complain of pain which comes on late after eating, and which is promptly relieved by the ingestion of food or soda. This is particularly true of the penetrating types of carcinomatous ulcers. On the other hand, the brevity of the history and the anacidity are not entirely inconsistent with the diagnosis of benign gastric ulcer. Usually, however, ulcers do not cause the severe symptoms manifested in this case.

In the following nine cases, the opinion of the surgeon, based on the gross pathologic appearance of the lesions at operation, was that a malignant condition was present. The gross pathologic appearance at times is deceptive, and further proof of the probability of diagnostic error in some of these patients is the fact that they are alive many years following the laparotomy at which the ulcer could not be excised.

CASE 3—A woman, aged 53, had suffered from dyspepsia for about fifteen years. During the first twelve of these years, trouble had been intermittent. During the last three years, she had had almost daily distress. Pain had come on between meals, but had been relieved promptly by the taking of sodium bicarbonate. Occasionally she had had nausea and vomiting with the pain, and occasionally she had vomited small amounts of blood. On a few occasions there had been severe crampy, epigastric pains. On the administration of a test meal, there was total acidity of 32 and free hydrochloric acid of 22, the quantity of gastric contents recovered was 148 cc. Roentgen examination disclosed a perforated gastric ulcer with hour-glass deformity. At operation, subacute perforating gastric ulcer with hour-glass contraction was found. The lesion looked malignant.

This patient's dyspepsia began when she was 38 years of age and continued for twelve years with the usual characteristics of ulcer. Then she began to have daily trouble, still with characteristics of ulcer, but with nausea and vomiting. At operation, a perforating ulcer with hour-glass contraction was found, the perforation probably was related



to the hour-glass contraction as cause to effect. Either of these complications could cause a slight change in symptoms. The symptoms of hour-glass stomach are not very definite, but usually, after this complication develops, the symptoms of nausea and vomiting supervene on the already established syndrome of ulcer.

CASE 4—A man, aged 64, had begun to have trouble with his stomach thirteen years prior to the time when he was seen at the clinic. Epigastric distress had come on at any time, meals frequently had aggravated it, and vomiting had come on at irregular intervals. He had been troubled with much belching and bloating. Eleven years previously he had had severe epigastric pain, and an emergency operation had been done. A gastric ulcer had been found and sutured. Following this, the patient had been fairly well for more than ten years. Then recurring symptoms like those experienced before the operation had developed. On gastric analysis there were found total acidity of 64, free hydrochloric acid of 36 and total quantity of 260 cc. Roentgen examination disclosed a perforated ulcer, on the lesser curvature, near the pylorus. At operation, a gastric ulcer was found which had perforated to the pancreas. The surgeon believed the ulcer to be carcinomatous.

In this case the ulcer had perforated eleven years prior to examination at the clinic. Emergency operation had been necessary to suture the perforation. For ten years thereafter the patient had felt well. Frequently perforation or brisk hemorrhage is followed by complete subsidence of dyspepsia or at least by a prolonged interval of freedom from symptoms.

CASE 5—A man, aged 38, for several years had had a sensation of much fullness, belching and slight pain coming on from two to three hours after his meals. He had spit up sour material several hours after eating. Pain at times had been referred from the epigastrium to the chest and back. On gastric analysis, total acidity had been found to be 70, free hydrochloric 48 and total quantity 150 cc. Deformity high on the lesser curvature had been found on roentgen examination. Operation revealed, high on the lesser curvature, an ulcer which was perforating to the pancreas. The operating surgeon believed the ulcer was malignant.

This patient gave a history that is not unusual in gastric ulcer. The pain in this instance was referred from the epigastrium upward into the chest and through to the back. This is usually significant of a penetrating lesion. The direction of reference of pain may be the same whether the lesion is gastric or duodenal. The ulcer in this case was found to have perforated to the pancreas.

CASE 6—A man, aged 45, came to the clinic complaining of dyspepsia which dated back twenty years. This is a definite characteristic of ulcer. During the last month the pain had been more severe. Frequently it had been referred through to the back and had been so severe it had doubled him up. He had obtained imperfect easing of symptoms by taking food or sodium bicarbonate. There had

been a recent loss in weight of 45 Kg. A large, perforating gastric ulcer was revealed by roentgen examination. This, at operation, was thought to have undergone malignant change.

Nothing suggestive of a malignant condition was found in this history. The symptoms started when the patient was 25 years of age. There were the usual characteristics of ulcer. The failure to get perfect ease from symptoms after ingestion of food or sodium bicarbonate is not unusual in the perforating types of ulcer. The ulcer was large, and it may have<sup>7</sup> been because of this that the diagnosis of malignancy was made. MacCarty has pointed out that chronic ulcers, whether simple or carcinomatous, vary greatly in size, shape and form. As a rule, most chronic gastric ulcers larger than 2.5 cm. in diameter are carcinomatous. This complication is less frequent in subacute perforating ulcers.

CASE 7—A man, aged 50, had had intermittent dyspepsia for eight years, with fewer periods of freedom lately. Distress had consisted of severe sharp, burning epigastric pain which had come on about two hours after meals and which had been relieved by the taking of food. Occasional vomiting, not of the retention type, had occurred. He had been severely constipated. In six years he had lost 18.1 Kg. in weight. On gastric analysis, total acidity was found to be 56, free hydrochloric acid 36 and the total quantity of gastric contents 185 cc. Roentgen examination revealed a large perforated ulcer on the lesser curvature, at the middle portion of the stomach. At operation, a large perforated ulcer was found which was thought to be malignant.

CASE 8—A man, aged 44, had had intermittent dyspepsia for nine years. Three years prior to examination at the clinic he had had an operation for ulcer of the stomach. He had been better following this, until two and a half months before he was seen at the clinic. During this two and a half months he had had epigastric distress at intervals, and at times severe pain which had been referred through to the back, and which had attained maximal intensity from one to one and a half hours after meals. He had had some headache and dizziness and had been severely constipated. Roentgen examination revealed a small ulcer high on the lesser curvature of the stomach. At operation a subacute gastric ulcer, probably malignant, was found.

CASE 9—A man, aged 54, had had dyspepsia for five years. Sometimes he had been comfortable for three or four weeks. From one-half to three hours after meals he had suffered from burning epigastric pain which had been relieved by the taking of food. He had not tried sodium bicarbonate. He had been nervous, had suffered some loss of weight and had been badly constipated. A large, perforated gastric ulcer, high on the lesser curvature, was evident by roentgen examination. At operation a perforating gastric ulcer was found which was too high to remove. Gastro-enterostomy was performed. The lesion looked malignant.

The three preceding cases can be considered collectively because the histories and operative observations are similar. The symptoms date back for from five to eight years and have the usual characteristics of

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<sup>7</sup> MacCarty, W. C. Chronic Ulcer and Carcinoma of the Stomach, *Am. J. M. Sc.* **173** 466, 1927.

ulcer intermittency, onset of pain late after meals and relief from the taking of food and sodium bicarbonate. In two instances, the ulcer was high on the lesser curvature, in the other instance, it was near the angle. The operating surgeons were of the opinion that the lesions were malignant, but specimens were not removed for diagnosis, and the data used as criteria of a malignant condition were not stated.

CASE 10—A man, aged 54, had had dyspepsia for six months, epigastric pain one and a half hours after meals and pain which waked him at night. He had obtained relief by the use of food and sodium bicarbonate. In two attacks of severe pain in the epigastrium, hypodermic medication had been required. After a test meal, total acidity of the gastric contents was 54, and free hydrochloric acid, 34, the quantity of content was 75 cc. Roentgen examination disclosed a perforated ulcer on the lesser curvature. At operation, a large ulcer on the lesser curvature, probably malignant, was found.

CASE 11—A man, aged 64, had had dyspepsia dating back ten months. There had been epigastric pain radiating into the chest, which had been relieved by the taking of food and sodium bicarbonate. He had suffered from much flatulence. Rarely, he had vomited sour material. There was qualitative food relationship. Sweets and fats had caused trouble. The results of gastric analysis were as follows: total acidity, 52, free hydrochloric acid, 32, quantity, 70 cc. A large, perforated gastric ulcer was revealed by roentgen examination. At operation an ulcer, probably malignant, was found.

In both of these cases, the history of dyspepsia was short, dating back ten months in one instance and six months in the other. Both patients were in the cancer age. In one instance, the history had all the characteristics of a rather severe penetrating type of peptic ulcer. The only suggestion of a malignant condition lay in the fact that symptoms of dyspepsia did not arise until the patient was 54 years of age. Too much significance should not be placed on the fact that dyspepsia does not begin until after the age of 50. It is not particularly unusual for symptoms which prove at operation to be due to a benign gastric ulcer to arise after that age. In case 11, there were symptoms which are more suggestive of a malignant condition than of benign ulcer. This patient had not had trouble with her stomach until the age of 63. There was some relief from pain by ingestion of food or sodium bicarbonate. This is not an uncommon experience of patients with carcinoma. There was much nausea and some vomiting. These symptoms were worse after the taking of sweets or fats.

Several facts stand out rather prominently after considering this group. In the first place, only one carcinoma was found in 700 cases in which the preoperative diagnosis of duodenal ulcer was made. In the gastric ulcer group, however, things were different. Although carcinoma was proved in only one of these cases it was suggested in some of the others. It is impossible to be absolutely certain preoperatively that any gastric ulcer is benign.

*Group 4*—Some of the lesions less commonly associated with ulcer in laparotomies undertaken after a clinical diagnosis of gastric or duodenal ulcer had been made are included in this group. The relative frequency of these lesions was found to be as follows: benign tumors, 0.3 per cent, duodenitis or gastritis, 0.5 per cent, diverticula, 0.3 per cent, miscellaneous, Lane's kink, splenitis and calcareous lymph node of the jejunum, one case each, 0.3 per cent, cases in which the opposite ulcer was found, 0.7 per cent. In three cases, benign tumors were present.

**CASE 12**—A woman, aged 30, for eight months prior to admission to the clinic had had attacks of severe pain in the upper part of the abdomen which had radiated from the epigastrium through to the left shoulder and for relief of which hypodermic medication had been necessary. Flatulence, nausea and vomiting had been associated with the pain. Attacks usually had come on suddenly, had lasted a few hours and had disappeared. Five months before coming to the clinic the patient had been operated on for disease of the gallbladder. At operation, the gallbladder was found to be normal in every way. On gastric analysis, total acidity was found to be 48, free hydrochloric acid, 28 and the quantity of gastric contents, 80 cc. A duodenal ulcer was revealed by roentgen examination. At operation a small ulcer, just below the pylorus on the anterior wall, chronic appendicitis, and a large pancreatic cyst adherent to the entire posterior surface of the stomach were found. The pressure of this large tumor on the posterior wall of the stomach can be seen plainly in the roentgenogram that was made before the operation.

The symptoms in this case are not those usually attributable to peptic ulcer. The ulcer was probably not the cause of the complaints of the patient. In this instance, reconsideration of the roentgenogram of the stomach disclosed the imprint of the tumor on the posterior wall of the stomach. If, in addition to the clinical history, this information had been available preoperatively, a correct diagnosis probably would have been possible. Unless a fluctuating tumor about the umbilicus is demonstrable, however, the diagnosis of a pancreatic cyst is extremely difficult. Even when a tumor is palpable, it may be difficult and frequently is impossible to be certain that its origin is pancreatic. Mesenteric cysts, tumors of the kidney or spleen, retroperitoneal tumors, and even ovarian cysts may be so difficult to differentiate, that the question cannot be settled by means of palpation and the most carefully taken history. Judd<sup>8</sup> reviewed records of forty-one pancreatic cysts at the Mayo Clinic. Regarding the complaint registered by these patients he stated:

The symptoms of the cyst usually are recorded as due to its pressure on adjoining organs. Pain is nearly always present and in our series of cases was more pronounced than in most of those formerly reported. If the tumor becomes

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8 Judd, E. S. Cysts of the Pancreas, *Minnesota Med.* 4:75, 1921.

large, it presses on the stomach causing indigestion and vomiting. Some of our patients had severe seizures of vomiting which we attributed to accompanying pancreatitis rather than to pressure. Pressure may be exerted on the diaphragm, colon and bile ducts. Jaundice is not usually present in these cases. Loss of weight was considerable in many instances.

Judd further pointed out the frequent relationship of cholecystitis and pancreatic cysts.

CASE 13—A man, aged 33, for eleven years had had long intervals of mild dyspepsia. He had the sensation that there was a lump in the stomach, and much fullness and bloating. The first pain, with characteristics of ulcer, had come on four years previous to examination. He had obtained ease with food and sodium bicarbonate. Night pain and melena had appeared two years prior to examination. The pain was located in the midepigastriac region, and on a few occasions had been very acute. On gastric analysis, the total acidity was found to be 76, and free hydrochloric acid, 56, the quantity of contents recovered was 120 cc. Roentgen examination revealed duodenal ulcer, and operation, in addition to the duodenal ulcer, revealed chronic appendicitis and a pedunculated fibroma of the jejunum.

In this case the discovery of a pedunculated fibroma of the jejunum was unexpected. The history was that of ulcer, and there were no symptoms which would have led any one to suspect the lesion which was found. Fibroma of the jejunum is an extremely rare condition. These tumors may grow into the lumen of the bowel or may push outward. The tumors which grow inward usually are small, but because of this position they may cause intestinal obstruction. The fibromas of the intestines which extend outward may become very large. Grossman<sup>9</sup> reported one arising from the transverse colon that reached the size of a man's head.

CASE 14—A man, aged 39, had had a complaint of the ulcer type for eleven years. Intervals of epigastriac pain and tenderness had come on late after meals or had waked him at night. He had obtained some ease by the use of food and sodium bicarbonate. He had suffered from much nausea and bloating but not from vomiting. Gastric analysis revealed total acidity of 68 and free hydrochloric acid, 50, the quantity of stomach contents recovered was 100 cc. Roentgen examination disclosed a duodenal ulcer. At operation, a duodenal ulcer and chronic appendicitis were found, a cystic tumor, which grew from the suspensory ligament of the liver, was also discovered.

The symptoms in this case were undoubtedly caused by the ulcer. There was nothing in the history nor in the general examination that might have suggested the presence of a cystic tumor which was found to have grown from the suspensory ligament.

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<sup>9</sup> Grossman, Paul. Quoted by Reichel, Paul, and Staemmler, Martin. *Die Neubildungen des Darmes*, Stuttgart, Ferdinand Enke, 1924, p. 258.

In 700 cases diagnosed as duodenal ulcer, preoperatively, duodenitis was found in five and gastritis in one. In the 450 cases in which operation was performed for gastric ulcer, gastritis was found only once.

CASE 15—A man, aged 32, for eighteen months had had intervals of dyspepsia lasting from two to three days. He described a dull pain in the epigastrium and right upper quadrant of the abdomen, associated with nausea and flatulence which came on from fifteen to thirty minutes after eating. There was a burning sensation in the stomach, eructation of gas and vomiting of small amounts of food shortly after eating. He was severely constipated. His symptoms had been gradually progressive. On gastric analysis, total acidity was found to be 94 and free hydrochloric acid, 74, the total quantity of gastric contents was 120 cc. Duodenal ulcer was found on roentgen examination. At operation, chronic appendicitis and an area of duodenitis were discovered. The gallbladder was normal.

CASE 16—A man, aged 40, had had dyspepsia for four years, with much belching and bloating after meals. Cabbage and turnips had caused him trouble. On two occasions he had had colicky pain in the upper part of the abdomen with residual soreness. During the year before admission to the clinic, epigastric pain had come on two hours after eating and had been relieved by the taking of sodium bicarbonate. On gastric analysis total acidity was found to be 68 and free hydrochloric acid, 48, the total quantity of gastric contents was 100 cc. The roentgen diagnosis was duodenal ulcer. Operation revealed chronic appendicitis and an area of duodenitis. The gallbladder was normal.

CASE 17—A man, aged 37, complained of periodic dull aching in the epigastrium coming on two hours after meals. The pain never was severe. Occasionally there was nausea but no vomiting. For several years he had had some anorexia and spells of dizziness. The blood count was within normal limits. Gastric analysis disclosed the following: total acidity, 88 and free hydrochloric acid, 76, a total of 80 cc of gastric contents was expressed. Duodenal deformity was disclosed at roentgen examination. The diagnosis was peptic ulcer, and at operation extensive duodenitis associated with multiple ulcers and chronic appendicitis was found. Duodenitis was found in resected tissue.

CASE 18—A woman, aged 62, had stomach trouble that had begun about a year previously. Two or three hours after meals she experienced an uncomfortable sensation of fulness which was relieved somewhat by the taking of sodium bicarbonate. She had slight pain just above the umbilicus which seemed "to go through her to the back." Fried foods made her symptoms worse. She had had much nausea and some vomiting, and she was constipated. Gastric analysis revealed total acidity of 80 and free hydrochloric acid of 60, the total quantity of stomach contents was 70 cc. Duodenal deformity was found at roentgen examination. The diagnosis was duodenal ulcer. At operation, a small duodenal ulcer and a considerable amount of duodenitis were found. The appendix gave evidence of chronic inflammation.

CASE 19—A man, aged 39, had had stomach trouble at intervals for nine years. He had pain in the midepigastrium which, late after eating, was severe and at times was colicky. Distress was frequently referred through to the back, and it was relieved by the taking of food and sodium bicarbonate. Three years before he came to the clinic, an ulcer had perforated the wall and the place had been sutured. Shortly after this operation dyspepsia of the ulcer type had again

developed. At intervals he had had hemorrhages. Roentgen examination disclosed duodenal ulcer. At operation chronic appendicitis, duodenal ulcer and an area of duodenitis were found.

In cases 15 and 16, definitely punched-out ulcers were not found at operation. Instead, an area of localized inflammation of the duodenum was apparent. Recently, one of us (Rivers)<sup>10</sup> reviewed a series of fifty-one surgically verified cases of duodenitis, gastritis and gastrojejunitis. It was suggested from this study that these shallow mucosal or submucosal lesions can be equal in importance with ulcer. A clear-cut syndrome characteristic of duodenitis could not be formulated. In a general way, the histories suggest ulcer, but in more than 50 per cent of the cases there is a liberal admixture of symptoms suggesting cholecystitis. Usually there is nausea, flatulence and vomiting, and frequently there is distress in the upper right quadrant, suggestive of a pathologic condition of the gallbladder. In cases 15 and 16, the history is that usually associated with cholecystitis, yet at operation evidence of this complication was not demonstrable. In cases 17, 18 and 19, both ulcer and duodenitis were found. In case 17, multiple ulcers and extensive duodenitis coexisted. In this case, the history includes some characteristics of ulcer, yet it is atypical since there was much complaint of nausea, dizziness and anorexia. In cases 18 and 19 there were the characteristics usually attributed to peptic ulcer.

CASE 20—A man, aged 54, gave a history of dyspepsia with characteristics of ulcer of ten years' duration. He had had pain in the epigastrium two or three hours after meals, and frequently he had had pain at night which was relieved as a rule by food. Sodium bicarbonate gave relief. For the period just before he came to the clinic he had belched a great deal. After a test meal, total acidity of the gastric contents was 50 and free hydrochloric acid, 30, the total quantity of gastric contents recovered was 340 cc. Roentgen examination disclosed an operable lesion at the pylorus. A diagnosis of pyloric lesion, probably duodenal ulcer, was made. At operation, marked thickening of the pylorus was found. About 2 cm. above this there was the crater of an ulcer. By microscopic examination, marked gastritis about the pylorus was demonstrable.

CASE 21—A woman, aged 47, for two years had had periodic attacks of nervousness and dyspepsia with much gas and nausea and some heartburn. These symptoms were somewhat worse after sausage and fried food had been eaten. On gastric analysis total acidity was 40 and free hydrochloric acid, 26, the total quantity of gastric contents was 200 cc. Roentgen examination disclosed a small ulcer on the lesser curvature near the pylorus. At operation, gastric ulcer was found. An excised portion of the stomach had the characteristics of chronic inflammatory tissue (gastritis?).

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10 Rivers, A. B. A Consideration of Certain Etiologic Factors and Clinical Manifestations of Inflammatory Lesions of the Stomach Over Duodenum, unpublished data.

In case 20, the history is characteristic of ulcer, and it covers a period of ten years. The recent development of some pyloric obstruction probably was responsible for the belching and bloating which became troublesome several months before operation. The obstruction in this instance was due to the inflammatory process extending to the pylorus and producing pyloritis. The roentgen appearance of the lesion had some characteristics of a malignant condition. In case 21, the history has more of the characteristics usually attributed to ulcer. The roentgen disclosure of a niche near the pylorus influenced the clinician in advising surgical measures. The symptoms of gastritis are extremely indefinite, nausea, vomiting, belching and aggravation of symptoms by certain types of food are the more frequent complaints. Pain usually is not severe. In our series, operation usually was advised because roentgen examination revealed deformities suggesting gastric ulcer or carcinoma.

In 0.37 per cent of patients operated on for peptic ulcer, a diverticulum of the small intestine also was found. Meckel's diverticulum was discovered twice, and on two occasions the diverticulum was found in the duodenum. In all of these cases, a preoperative diagnosis of duodenal ulcer had been made.

**CASE 22**—A man, aged 41, entered the clinic because of periodic attacks of cramping epigastric pains associated with nausea and vomiting. He had been troubled in this way for twenty years. Attacks usually had continued for five or six days. At times, the pain had been severe. Occasionally he had had pain also in the lower right quadrant of the abdomen. Gastric analysis disclosed total acidity of 102 and free hydrochloric acid, 82, the total quantity of gastric contents recovered was 100 cc. A duodenal ulcer was found on roentgen examination. At operation, perforating duodenal ulcer and chronic appendicitis were found. In the ileum, about 183 cm from the ileocecal valve, there was a Meckel's diverticulum.

**CASE 23**—A man, aged 35, had suffered from intervals of distress in the upper portion of the abdomen for seven years. He had had pain in the epigastrium and upper right quadrant which had waked him at night or which had come on from three to four hours after meals. There had been some belching, bloating and vomiting, which sodium bicarbonate or food usually relieved. He had been getting progressively worse for six months with more pain and shorter intervals of relief from symptoms. After a test meal, total acidity was 40 and free hydrochloric acid, 26, the total quantity of gastric contents was 180 cc. Roentgen examination revealed duodenal ulcer. At operation, subacute duodenal ulcer, chronic appendicitis and a Meckel's diverticulum were found.

In case 22, the diverticulum was found about 183 cm from the ileocecal valve. It is unusual to find a Meckel's diverticulum further than 91.4 cm from the ileocecal junction. In all probability, the diverticulum in the cases cited in this paper had nothing to do with the symptoms. Occasionally a Meckel's diverticulum causes serious complications, acute inflammation with perforation may result, intussusception may originate in a Meckel's diverticulum, and occasionally it may cause



intestinal obstruction by kinking the bowel After studying a series of such cases, Balfour<sup>11</sup> stated

Meckel's diverticulum and its associated conditions should be borne in mind in obscure inflammatory processes of the lower abdomen, and especially in those cases of supposed acute appendicitis in which the appendix does not appear to be sufficiently involved to explain the symptoms, the ileum should be explored for a possibly acutely inflamed Meckel's diverticulum

CASE 24—A man, aged 48, gave a history that dated back twenty-seven years The symptoms were characteristic of peptic ulcer The pain was referred through to the back Symptoms were worse after eating acid food or fats Estimation of gastric acidity disclosed hyperchlorhydria A duodenal deformity was noted by the roentgenologist At operation, two duodenal ulcers and a duodenal diverticulum were found, the lower side of the diverticulum was attached to the pylorus Chronic appendicitis also was found

CASE 25—A man, aged 45, for about nineteen years had had intervals of dyspepsia two or three hours after meals and there had been burning pain in the epigastrium, which was promptly relieved by the taking of food or sodium bicarbonate Frequently he had been awakened at night by pain in the epigastrium Brief periods of dieting had given relief for prolonged periods There had been much belching and bloating during the attacks of pain Gastric analysis revealed total acidity of 54 and free hydrochloric acid, 40, the total quantity of gastric contents was 50 cc A duodenal ulcer was disclosed at roentgen examination Lesions found at operation were as follows duodenal ulcer with considerable contraction, dilation of the stomach, chronic appendicitis and a diverticulum 2 cm long on the inferior margin of the duodenum

The duodenal diverticula discovered in these cases probably in no way influenced the symptoms, which were quite characteristic of ulcer in both cases We know of no syndrome or complaint regularly attributable to the presence of diverticula which would aid in diagnosing this condition Duodenal diverticula usually can be divided into two types, developmental and acquired Diverticula of the developmental type probably form at weak points in the bowel They are situated within a radius of 3 cm of the ampulla of Vater and usually are found incidentally at necropsy In a series of cases reviewed at the clinic, apparently none of the developmental diverticula gave rise to symptoms Nagel<sup>12</sup> studied nineteen cases of acquired duodenal diverticula These were all in the first portion of the duodenum

Three were found associated with gallbladder disease, in two of which the diverticulum appeared to have formed as a result of closure of a fistulous tract between the two organs In one of the patients, gallstones were present in the diverticulum Two diverticula were in patients operated on for chronic appen-

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11 Balfour, D C Meckel's Diverticulum A Report of Fifteen Cases, *Journal-Lancet* **31** 110, 1911

12 Nagel, G W Unusual Conditions in the Duodenum and their Significance Membranous Obstruction of the Lumen, Diverticula and Carcinoma, *Arch Surg* **11** 529 (Oct) 1925

ditis and in whom the traction of adhesions around the duodenum were probably the factors producing the diverticula. The fourteen remaining were definitely associated with duodenal ulcer. The majority form just beyond the pylorus in the antero-inferior portion of the duodenum. All coats of the bowel are included in their walls and they are not due to a perforation of the base of an ulcer and resulting formation of a false pouch, but are formed by the contraction of scar tissue and pressure from within the bowel.

As miscellaneous cases, we have included one each of Lane's kink, splenitis and calcareous lymph node of the jejunum. These complications were found during laparotomy for gastric ulcer.

CASE 26—A man, aged 39, entered the clinic because of chronic constipation. Occasionally there was nausea shortly after eating. There was an uncomfortable sensation of fulness in the upper part of the abdomen but no pain. The symptoms were mild and did not incapacitate the patient for his work. Gastric analysis disclosed total acidity of 40 and free hydrochloric acid of 20, 180 cc of gastric contents were recovered. A gastric ulcer, with some retention, was recognized at roentgen examination. At operation, in addition to gastric ulcer and chronic appendicitis, a Lane's kink was found.

There is no information in this history which would lead one to suspect that this patient might have gastric ulcer, chronic appendicitis and Lane's kink. In fact, all the complaints easily could have been caused by the chronic constipation. It might be assumed that the Lane's kink, a developmental condition resulting from fixation by bands of the terminal 91 cm of the ileum, was responsible for the symptoms.

For several years, considerable importance was attached to the presence of Lane's kink in the ileum. Various operations were devised and performed to liberate or circumvent the alleged obstruction caused by this condition, and although a few patients probably were improved in condition, many more were no better, and not a few were decidedly worse after such surgical procedures.

CASE 27—A woman, aged 40, gave a history of intermittent stomach trouble of seven years' duration. At intervals, the pain had become sharp, had been referred from the epigastrium to the back and occasionally had extended upward to the left shoulder. The distress usually had come on about an hour after meals, and the taking of more food had relieved it temporarily. She had been comfortable on a milk diet. Migraine and constipation had been associated with the other symptoms. She had lost 181 Kg in four years. Gastric analysis revealed total acidity of 40 and free hydrochloric acid, 32, 160 cc of gastric contents were recovered. Results of a roentgen examination were negative. A diagnosis of peptic ulcer was made. At operation a gastric ulcer and chronic appendicitis were found. A degenerating calcareous lymph node was removed from the mesentery of the jejunum.

The history in this case presents the usual characteristics of ulcer. The degenerating calcareous lymph node which was found on the jejunal mesentery is not of particular clinical significance.

CASE 28—A man, aged 43, began having dyspepsia eighteen years prior to his examination at the clinic. He described intermittent pain situated about the umbilicus, coming on two or three hours after eating. Food relieved the pain. Early in the history he had had gastric hemorrhages on two occasions. The symptoms, after persisting for ten months, had disappeared, and the patient had remained well for fifteen years. Three years, and again one year, before coming to the clinic he had had a brief period of recurrent trouble. During the two months prior to his visit to the clinic, he had had daily pain in the epigastrium, which had come on two or three hours after eating and which had been relieved by taking sodium bicarbonate. He had been markedly constipated. Roentgen examination revealed gastric and duodenal deformities. Estimation of gastric acidity disclosed slight hyperchlorhydria. At operation perforated gastric ulcer, chronic duodenal ulcer, chronic pancreatitis, chronic splenitis and chronic appendicitis were found. Partial gastrectomy, splenectomy and appendectomy were performed. Convalescence was uneventful.

The history in this case was characteristic of ulcer and included hemorrhages. Whenever the operating surgeon is not entirely certain that bleeding comes from a definitely active ulcer, a thorough search for extragastric causes for it is obligatory. In this case, splenitis was discovered and the spleen was removed, thus possibly avoiding a subsequent operation. The spleen may be instrumental in several ways in the production of gastro-intestinal hemorrhage: (1) in a mechanical way, by causing venous engorgement of the mucous membrane of the stomach secondary to thrombophlebitis of the splenic veins, and (2) by serving as a focus in activating hepatic cirrhosis, which in turn, of course, is a frequent cause of bleeding from the stomach.

In going over the records of the 1,075 cases included in this series, it may be noted that seven patients with a preoperative diagnosis of duodenal ulcer were found at operation to have ulcers only in the stomach.

CASE 29—A man, aged 39, gave a good history of ulcer of three years' duration. He complained of pain in the epigastrium and in the upper left quadrant and reported relief from the taking of food and sodium bicarbonate. Shortly before he came to the clinic he had vomited large amounts of watery material. After a test meal, total acidity was 84 and free hydrochloric acid, 60, the total quantity of gastric contents recovered was 130 cc. Results of roentgen examination of the stomach were negative. A diagnosis of duodenal ulcer was ventured. At operation, chronic appendicitis and a chronic gastric ulcer, 5 cm. above the pylorus, were found.

CASE 30—A man, aged 36, gave a history of having had, for seven years, dyspepsia of a type suggestive of ulcer. This included epigastric pain which came on one and a half to two hours after meals, and which radiated through to the back. Taking of food and of sodium bicarbonate relieved this pain. He had had some pain at night. Inadequate relief had been obtained from the type of diet employed for ulcer. Gastric analysis revealed total acidity of 80 and free hydrochloric acid of 60, the total quantity of gastric contents recovered was 300 cc. The gastric contents contained undigested remnants of food. Diagnosis by roentgen methods was indeterminate. A diagnosis of duodenal ulcer was made.

At operation, a gastric ulcer and chronic appendicitis were found. The ulcer was situated on the lesser curvature about one third of the way from the pylorus to the cardia.

CASE 31—A man, aged 55, complained of distress which was characteristic of ulcer and which had troubled him over a period of six years. At first, there had been prolonged periods of freedom from symptoms, but later the distress had occurred daily. During the year prior to examination at the clinic, he had had much flatulence but no vomiting. After a test meal, the total acidity was 80 and the free hydrochloric acid, 60, 250 cc of gastric contents were recovered. Roentgenographically, a lesion was evident in the pyloric ring. A diagnosis was made of pyloric obstruction, probably caused by duodenal ulcer. At operation, a subacute gastric ulcer was found 3 cm above the pylorus. Microscopic study of the tissue showed a simple gastric ulcer.

CASE 32—A man, aged 55, had had dyspepsia for fourteen years. In the history were the usual characteristics of ulcer: at first, prolonged periods of freedom from distress, more recently, almost daily trouble. The pain never had been very severe, and food usually had relieved him temporarily. A perforated duodenal ulcer was found at roentgen examination. At operation, a perforating gastric ulcer was found near the pylorus, it did not appear to be malignant.

CASE 33—A man, aged 56, had had dyspepsia for nine years. Nausea had come on two hours after eating. More recently he had had much gas and bloating one and a half hours after meals, and occasionally he had vomited. He had obtained relief after taking food or sodium bicarbonate. He had not suffered much pain. After a test meal there was total acidity of 70 and free hydrochloric acid of 52, 120 cc of gastric contents were recovered. A duodenal deformity was evident on roentgen examination. At operation, a gastric ulcer was found 3 cm from the pylorus, the stomach was dilated, hepatitis and chronic appendicitis also were found, the gallbladder was normal.

CASE 34—A man, aged 42, had had dyspepsia at intervals for eight years. Epigastric pain usually had come on two hours after meals although it might occur while he was eating. Sodium bicarbonate had no effect on it. When pain was at its maximum, he had become nauseated and at times had vomited. After a test meal, total acidity was 76 and free hydrochloric acid, 60, 305 cc of gastric contents were recovered. Roentgen examination disclosed duodenal deformity. At operation, the patient was found to have subacute appendicitis and a gastric ulcer in the median portion of the lesser curvature.

CASE 35—A woman, aged 52, had had dyspepsia for two years with anorexia, nausea shortly after meals, vomiting and constipation. There had been no pain. After a test meal, total acidity was 60 and free hydrochloric acid, 42, 350 cc of gastric contents were recovered. A duodenal deformity was found on roentgen examination. At operation gastric ulcer was found, with much inflammation extending to the pylorus and duodenum.

In these cases, 29 to 35, there were definite characteristics of ulcer in the history. In case 29 a deformity was not found by roentgen examination in either the stomach or duodenum. In case 30, the roentgen diagnosis was indeterminate. These histories were characteristic of ulcer, and the estimation of gastric acidity revealed hyperchlorhydria. From the data available, the clinician was not justified in making a more specific diagnosis than peptic ulcer. In case 31, the diagnosis of

carcinoma was not excluded. It has been pointed out by many observers that it is impossible from the history alone to differentiate gastric and duodenal ulcer. The clinician, in these instances, probably was influenced in making the diagnosis of duodenal ulcer for no other reason than that by surgical methods it has been proved to be far more common than gastric ulcer. In cases 31, 33 and 34, the histories were excellent examples of those found when peptic lesions are present, and the roentgenologists made diagnoses of duodenal ulcer. This should have been sufficient evidence to warrant the clinicians' diagnosis of duodenal ulcer. Carman,<sup>13</sup> in discussing the accuracy of roentgen diagnosis, stated that in a series reviewed by him roentgen diagnosis was correct in cases of peptic ulcer in 98.21 per cent, whereas in the localization of ulcer it was correct in more than 95 per cent.

It is difficult to distinguish any feature suggesting peptic ulcer, clinically, in case 35. In view of the extensive inflammatory reaction involving the pylorus and duodenum, it is not difficult to understand why a roentgenologic error was made in this case. In a paper dealing with the limitations of roentgenologic diagnosis, Carman<sup>14</sup> wrote "Lesions near the pylorus are often lacking in differential signs and it may be impossible to determine whether the distortion of the pyloric region is due to a small carcinoma, a gastric ulcer, a duodenal ulcer with extensive adhesions or a syphilitic lesion."

The errors in diagnosis illustrated in this group are not of any great significance. These cases were analyzed separately because we wanted to know not only what the operative data were when the major lesion seemed preoperatively to be either gastric or duodenal ulcer, but also whether these histories contained evidence which should have made clinicians suspect the conditions which remained undiagnosed.

#### SUMMARY AND CONCLUSIONS

1. The lesions found in association with ulcer when this has been considered the condition of major importance have been studied, and their relative frequency has been outlined graphically in figure 1.

2. More careful evaluation of symptoms and painstaking general examination of the patient undoubtedly would be followed by greater accuracy in diagnosis. Associated acute or subacute appendicitis should, under these conditions, be recognized much more frequently. That greater accuracy in diagnosis would benefit the patient seems hardly questionable. The better we understand all the factors influencing the

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13 Carman, R. D. The Roentgen Diagnosis and Localization of Peptic Ulcer, *California State J. Med.* **18** 377, 1920.

14 Carman, R. D. Limitations of Roentgenologic Diagnosis, *New York State J. Med.* **22** 302, 1922.

symptoms under consideration, the more intelligently suitable measures for relief can be instituted

3 In discussing the advisability of adopting surgical methods in the treatment of patients with peptic ulcer because of the probability of finding associated lesions of importance, one must make distinctions, for this reason, it is obligatory to consider gastric and duodenal ulcer separately

Analysis of chart 2, which includes only those cases diagnosed as instances of duodenal ulcer, shows that in but a single instance was a malignant condition found as a complicating lesion. The patient had pyloric obstruction, obviously a complication, and for treatment surgical procedures would without question be advised

The associated observation of chronic appendicitis should not be considered of great importance because it is extremely doubtful that the presence of this complication was in any way contributory to the symptoms from which these patients sought relief

The finding of acute or subacute appendicitis is undoubtedly of definite importance. That occasionally acute appendicitis may be masked by complicating ulcer, so that its presence will remain unsuspected, seems possible. It seems, however, that this complication usually would present features sufficiently definite to be indicative of its presence and that failure to find it is likely to be due to remiss methods of diagnosis or inattention to details by the examining clinician or surgeon

Rare complications, such as gastric ulcer associated with diverticula in the ileum or duodenum and with benign tumors, are not of paramount importance, and it would seem, therefore, that one is hardly justified in allowing the probability of finding important associated disease to exert any influence in deciding on the advisability of adopting surgical measures for ulcers, when otherwise a medical regimen might be the treatment of choice

With gastric ulcers, however, the probability of finding serious complications is a little greater. There is always the disquieting possibility that the ulcer under consideration is malignant. In 21 per cent of these cases, the surgeon found lesions with some characteristics of malignancy. Since there was no preoperative suggestion by clinicians that the lesion might be malignant, this seems of greater significance than otherwise. In about 50 per cent of the histories in this group one can find evidence which should have made the clinician suspicious of carcinoma. In some cases, the surgeon's assumption that a malignant condition was present probably was made on insufficient evidence, because a few of these patients are living and apparently are in good health despite the fact that the lesions were not removed at the time of the operation

The fact remains, however, that we do not have criteria which can be relied on to reassure us that any gastric ulcer is not potentially

malignant This fact cannot be ignored when the advisability of various types of treatment for gastric ulcer is under consideration

4 Consideration of rare complications of peptic ulcer which were not diagnosed preoperatively disclosed five cases complicated by duodenitis or gastritis, two by Meckel's diverticulum, two by duodenal diverticulum, and one each by Lane's kink, splenitis, calcareous lymph node of the jejunum, pancreatic cyst, fibroma of the jejunum and cyst of the suspensory ligament of the liver In seven instances, in which duodenal ulcer was diagnosed, gastric ulcers only were found at operation Great significance should not be attached to the finding of most of these lesions There was no pathologic feature of great importance in this entire group except for the cases of splenitis and pancreatic cyst It seems unlikely that the most careful evaluation of symptoms and objective observations would have sufficed to make an accurate diagnosis in most of these cases

5 When at least the more frequent of the lesions associated with peptic ulcer are borne in mind, the probability of accurate diagnosis should be increased This added efficiency would make the clinician increasingly authoritative in his opinions regarding the advisability of various therapeutic procedures

# THE PITUITARY GLAND AND THE SUPRA- RENAL CORTEX \*

ROBERT C MOEHLIG, M D

DETROIT

The pituitary gland is functionally related to the suprarenal cortex, and this relationship can be understood from embryologic considerations. There can be no question but that glandular interrelationships have made it difficult to understand many problems in endocrinology. As Hoskins <sup>1</sup> has shown, there are almost innumerable combinations possible between the endocrine glands. It is, therefore, with some hesitancy that a discussion is undertaken to point out a particular correlation. The explanation to be offered finds its strength in its agreement with the known clinical, pathologic and experimental facts, and is based on sound fundamentals of embryology.

Aplastic states of the pituitary gland are concomitant with aplasia of the suprarenal cortex and, conversely, hyperplasia of the pituitary gland results in hyperplasia of the suprarenal cortex.

From the clinical side, the best examples of the aplastic and deformed pituitary are found in anencephalic fetuses. Hemicephaly, oxycephaly and other developmental defects are accompanied at times by developmental defects of the pituitary gland.

Ballantyne <sup>2</sup> described forty-five anencephalic fetuses and stated that the pituitary gland rarely was present. Schwalbe, <sup>2</sup> Haberfeld <sup>2</sup> and Wrege, <sup>2</sup> on the other hand, found that the pituitary gland was present.

Mauksch <sup>3</sup> found that the gland was present but abnormal, in some cases it consisted of only two lobes. Browne <sup>4</sup> found no trace of a pituitary gland in five anencephalic fetuses. Covell <sup>5</sup> studied thirty-two anencephalic fetuses and concluded that the pituitary is extremely variable in weight, being less than normal, the pars nervosa is lacking in the majority of cases, the pars intermedia is variable as to both occurrence

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\* From the Department of Internal Medicine, Harper Hospital, Detroit

1 Hoskins, R G. Recent Work on Internal Secretions, *Endocrinology* 6:621 (Sept.) 1922

2 Cited by Covell (footnote 5)

3 Mauksch. Das Verhalten der Hypophyse und des Canalis Craniopharyngeus in neun Fällen von Kranioschisis untersucht, *Anat. Anz.* 54:248, 1921

4 Browne, F J. The Anencephalic Syndrome in Its Relation to Apituitarism, *Edinburgh M. J.* 25:296, 1920

5 Covell, W P. Quantitative Study of Hypophysis of Human Anencephalic Fetus. *Am. J. Path.* 3:17 (Jan.) 1927



and volume Kraus<sup>6</sup> found that the most frequent developmental anomalies of the pituitary gland are seen in anencephalus, with the posterior lobe frequently absent Barlow<sup>7</sup> also found apituitarism in anencephalic fetuses Kiyono,<sup>8</sup> studying the pathologic anatomy of the endocrine glands in anencephalus, found striking pituitary defects Pituitary defects are, therefore, a frequent observation in anencephalus

It has long been known that aplastic states of the suprarenal cortex accompany cerebral defects, such as anencephalus and acrania, as well as some forms of hydrocephalus Several authors hold the opinion that the defect of the suprarenal cortex is responsible for defect of the brain (Alexander<sup>9</sup>), whereas others believe that the cerebral defect is responsible for the suprarenal condition (Weigert,<sup>9</sup> Kern,<sup>9</sup> Myers,<sup>9</sup> Landau,<sup>9</sup> Kohn,<sup>9</sup> etc.) Myers<sup>9</sup> has disproved the theory that the suprarenal cortex is responsible for the cerebral defect He showed that there is no developmental defect of the suprarenal cortex in anencephalic fetuses before the fifth month

Among older writers, Zander<sup>10</sup> and Weigert<sup>9</sup> made the singular observation that the suprarenal cortex is aplastic only when the anterior portion of the brain is involved in anencephalus One may accept the statement from the present knowledge of the facts that the anterior cerebral defects have involved the pituitary gland through its anatomic location

In all these cases of cerebral defect only the suprarenal cortex is involved, whereas the medullary portion of the suprarenal is normal

In some cases (Landau<sup>9</sup>), the suprarenal cortex was entirely missing According to Dietrich and Siegmund,<sup>11</sup> there is no regular parallelism between the degree of the cerebral defect and that of the defect of the suprarenal cortex, and there is no clear explanation Certainly, one must modify one's views to the opinion that the degree of defect of the suprarenal cortex is dependent on the degree of involvement of the pituitary gland and not related to the cerebral defect per se

Kohn<sup>12</sup> has recently taken the view that the pituitary gland is the responsible factor for the defect of the suprarenal cortex From his

6 Kraus, E J In *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol 8, p 810

7 Barlow, D L Apituitarism and the Anencephalic Syndrome, *Brit M J* **1** 15, 1923

8 Kiyono Pathologische Anatomie der endokrinen Organen bei Anenzephalie, *Virchows Arch f path Anat* **257** 441, 1925

9 Cited by Dietrich and Siegmund (footnote 11)

10 Zander, R Ueber functionelle und kinetische Beziehungen der Nebennieren zu anderen Organen, speziell zum Grosshirn, *Beitr z Physiol* **7** 489, 1890

11 Dietrich, R, and Siegmund, J, in *Handbuch der speziellen pathologischen Anatomie und Histologie*, 1926, p 951

12 Kohn, A Anenzephalie und der Nebennieren, *Arch f Entwicklungsmech d Organ* **102** 113, 1924

histologic studies of anencephalic fetuses, he noted that the epithelial portion of the pituitary gland was involved, there being scarcity of oxyphil and large basophil cells. Defects were noted in the infundibulum and pars nervosa. He based his opinion concerning the relationship of the pituitary gland and the suprarenal cortex on the well known clinical examples of pituitary atrophy (such as seen in pituitary dwarfism) with concomitant atrophy of the suprarenal cortex. He, therefore, placed the primary responsibility on the pituitary gland.

Further clinical proof of this relationship is furnished by cases of hypopituitarism, such as dystrophia adiposogenitalis, in which the pituitary disturbance is accompanied by various degrees of atrophy and aplasia of the suprarenal cortex. Postmortem studies of these cases have shown atrophy of the suprarenal cortex (Falta,<sup>13</sup> Kraus,<sup>6</sup> and others). Dietrich and Siegmund<sup>11</sup> called attention to the well known association of atrophy of the pituitary gland and of the suprarenal cortex.

Experimental proof of the rôle of the pituitary gland in atrophy of the suprarenal cortex has also been provided. Smith,<sup>14</sup> by hypophysectomy in the rat, produced a hypoplasia of the suprarenal cortex. The cortex is sensibly reduced in volume. The medulla is slightly if any altered. Landau<sup>9</sup> found the suprarenal cortex to be of this type in anencephalus.

Askoli and Legnani<sup>15</sup> found hemorrhages in the suprarenal cortex and an altered fat content after hypophyseal extirpation experiments.

Reichert<sup>16</sup> reported that the suprarenal glands of his puppies on which hypophysectomy had been performed were smaller than those of the controls.

The reverse picture has also been demonstrated. Falta,<sup>13</sup> in defining acromegaly, says (in italics) that one finds apparently "frequently hyperplasia of the suprarenal cortex." Fischer<sup>17</sup> found enormous suprarenal glands, the enlargement especially affecting the cortex. Fischer and Schultze<sup>18</sup> found enlargement of the suprarenal glands in two cases of acromegaly, in one of which the glands were at least five times the

13 Falta, William. *The Ductless Glandular Diseases*, Philadelphia, P. Blakiston's Son & Company, ed 2, 1916, p 235.

14 Smith, P. E. Disabilities Caused by Hypophysectomy and Their Repair, Tuberal (Hypothalamic) Syndrome in Rat, *J. A. M. A.* **88** 158 (Jan 15) 1927.

15 Askoli and Legnani, cited by Kraus (footnote 6).

16 Reichert, F. The Results of Replacement Therapy in an Hypophysectomized Puppy, **12** 451 (July-Aug.) 1928.

17 Fischer, B. Hypophyse und Akromegalie, *Frankfurt Ztschr. f. Path.* **11** 130, 1912.

18 Fischer, B., and Schultze, F. Zur Lehre von der Akromegalie und Osteoarthropathie hypertrophisierende, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **24** 607, 1912.

normal size Basso<sup>19</sup> said that the suprarenal glands have often been found enlarged at necropsy He quoted Amsler, Ausch, Eltester and Schroeder, Mullaly, Horbitz and others as saying that large suprarenal glands are found in acromegaly

It has been shown that acromegaly is associated at times with tumors of the suprarenal cortex

According to Kraus,<sup>6</sup> the hypertrophy of the suprarenal glands is due to hyperplasia of the pituitary eosinophil cells, whereas hypoplasia of these cells produces atrophy of the suprarenal glands

Hofstatter<sup>20</sup> was able to produce hypertrophy of the suprarenal cortex by injections of posterior lobe extract He used rabbits for his experiments, and the changes were noticeable around the thirtieth day

In analyzing the data submitted, one is forced to the conclusion that pituitary disturbances affect the suprarenal cortex and not the suprarenal medulla

The explanation of these correlations can be found in an analysis of the embryologic relationships I<sup>21</sup> have shown elsewhere that the pituitary gland has a selective action on mesenchymal tissues

Attention is called to the fact that the suprarenal cortex is a mesenchymal tissue in contrast to the suprarenal medulla, which is an ectodermal tissue<sup>1</sup>

Some of the relationships between the pituitary and mesenchymal tissues are obvious and need not be discussed No emphasis is needed, for instance, to show the relationship of the pituitary gland to bone and cartilage Its relationship to fat metabolism is also undisputed and while its exact *modus operandi* is still unknown, nevertheless it has a definite place in fat metabolism It is a natural sequence of thought that, if the suprarenal cortex reflects the state of the pituitary gland, the cholesterol metabolism would be involved A discussion of this relationship must be left for the future, but the importance is obvious

The selective action of the posterior pituitary extract when injected hypodermically is exerted on three mesenchymal tissues, it produces a contraction of the blood vessels, contraction of smooth muscle, such as that of the bladder and intestine, and a varying effect (diuresis or anti-

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19 Basso, P *Acromegaly, Endocrinology and Metabolism*, New York, D Appleton & Company, 1922, vol 1, p 809

20 Hofstatter, R *Ueber Befunde bei hyperhypophysierten Tieren*, *Monatschr f Geburtsh u Gynak* 19 387, 1919

21 Moehlig, R *Embryohormonic Relations of Pituitary Gland to Mesenchymal Tissues*, *Ann Int Med* 1 563 (Feb) 1928, *Embryohormonic Relations of the Suprarenal Cortex to Mesothelial Tissues*, *ibid* 1 563, 1928, *Selective Action of the Suprarenal Cortex Secretion on Mesothelial Tissues*, *Am J M Sc* 168 553, 1924 Moehlig, R, and Ainslee, H B *Pituitary Gland and Cholesterol Metabolism*, *Ann Clin Med* 5 772, 1927

diuresis) on the renal cells. Other articles<sup>21</sup> have gone into more detailed discussion concerning this selective action.

It was also shown that the suprarenal cortex has a selective action on a specialized part of the mesoderm, the mesothelium from which the sex glands and skeletal musculature are derived. On the basis that with involvement of the pituitary gland there is a concomitant involvement of the suprarenal cortex, these mesothelial tissues must also be considered to share in the symptomatology and pathology. This is, of course, a well known clinical fact, illustrated by many clinical examples, such as dystrophia adiposogenitalis with the involvement of the sex gland and muscular fatigue. In the anencephalic fetuses with pituitary anomalies, one should see the symptoms of apituitarism with the involvement of the mesenchymal tissue. The *British Medical Journal*,<sup>22</sup> in a comment on Biowne's work with anencephalic fetuses, states that the most rigorous search on the basis crani of his anencephalic fetuses revealed absolutely no trace of a pituitary gland. The syndrome with obesity, hypoplasia of the suprarenal glands and genital organs and stunted growth of body and limbs, agrees in the main with features of the condition called apituitarism.

It is to be noted that the embryohormonic relations of the pituitary to mesenchymal tissues, will explain the involvement of the suprarenal cortex.

#### SUMMARY

Anencephalus is accompanied by pituitary anomalies. The degree of anomaly varies in different cases, being greatest in anterior cerebral defects. The suprarenal cortex reflects the state of the pituitary gland and is always hypoplastic when the pituitary is involved in anencephalus. Hyperplasia of the pituitary gland results in hyperplasia of the suprarenal cortex.

The view that cerebral defects are responsible for aplasia of the suprarenal cortex must be modified to the view that the pituitary gland is the responsible factor.

It is to be emphasized that only the suprarenal cortex and not the medulla is involved in these pituitary anomalies, and the same holds true for experimental hypophysectomy.

The embryohormonic relation of the pituitary to mesenchymal tissues gives a clearcut explanation of this singular involvement.

The importance of the relation of the pituitary gland to the suprarenal cortex is readily realized when cholesterol metabolism is considered. Many related problems can be studied with a newer and better foundation.

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<sup>22</sup> Editorial, Brit M J 2 828, 1920

# THE EFFECT OF UNCOOKED STARCHES ON THE BLOOD SUGAR OF NORMAL AND OF DIABETIC SUBJECTS II \*

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In previous work,<sup>1</sup> raw starch was administered by mouth to rabbits as a means of studying pancreatic function and upper intestinal digestion. In these animals, a rise in blood sugar was uniformly produced, the average rise in the rabbits amounted to 62 mg per hundred cubic centimeters. This elevation of blood sugar is dependent on the liberation of dextrose from the starch molecule, and the hyperglycemia was shown to afford a means of estimating the activity of pancreatic diastase, on the one hand, and under conditions in which diastatic ferments are normally present, a means of studying other factors which influence the rate of digestion of starch in the alimentary canal.

*The Effect of 2 Gm of Raw Starch Per Kilogram of Body Weight on the Blood Sugar of Normal Dogs (Administered by Stomach Tube in 200 Cc of Water)*

	Blood Sugar, Mg per 100 Cc			
	Before	After One-Half Hour	After One Hour	After Three Hours
Dog, 15 Kg, 30 Gm raw starch	0 097	0 185	0 131	0 121
	0 105	0 140	0 150	0 117
Dog, 11 4 Kg, 23 Gm Starch	0 089	0 138	0 143	0 115

Approximately 5 Gm of starch per kilogram of body weight was used in rabbits. Three tests were performed on dogs to which 2 Gm of starch per kilogram of body weight was given. With this quantity, rises in blood sugar occurred which were comparable to those obtained in rabbits, as shown in the accompanying table.

Several workers<sup>2</sup> have employed cooked starch to obtain sugar tolerance curves in human subjects, and Maclean found that 50 Gm of

\* Submitted for publication, March 10, 1929

\* From George Washington University Hospital and the Hygienic Laboratory

1 Rosenthal, S M. Pancreatic Function and Upper Intestinal Digestion, Arch Int Med **41** 867 (June) 1928

2 Maclean, H. Glycosuria and Diabetes, London, Constable & Co., 1924  
Grav, H. Blood Sugar Standards, Arch Int Med **31** 241 (Feb) 1923  
Rowe, A H, and Rogers, H. Carbohydrate Tolerance in Normal Persons and in Nondiabetic Patients, Arch Int Med **39** 330 (March) 1927

cooked oatmeal, rice or potatoes would produce a rise in blood sugar comparable to 50 Gm of dextrose. However, when we gave from 50 to 75 Gm of raw starch to a group of patients, there was a striking absence of increase in blood sugar.

#### METHOD AND RESULTS

Soluble starch prepared according to Lintner was used. It was stirred into 250 cc of water, and 2 cc of normal (36 per cent) hydrochloric acid was added just before it was given. The acid makes the mixture more palatable and on theoretical considerations would prevent any digestion of the starch by the saliva. However, previous work on rabbits and further work on human beings indicate that no appreciable salivary digestion of uncooked starch takes place, for the effects on blood sugar were the same when acid was omitted as when it was employed. It will be interesting to know whether salivary digestion takes place to a greater extent in cases of gastric anacidity.

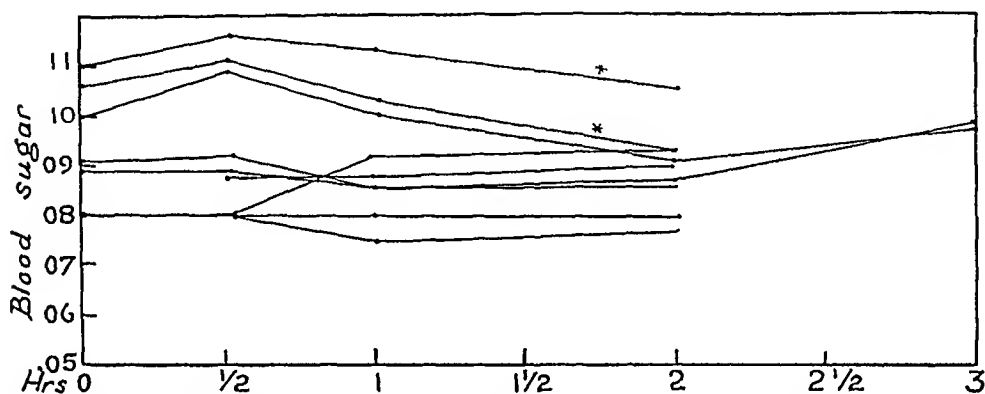


Chart 1—The effect on the blood sugar of normal adults of from 50 to 75 Gm of raw starch administered by mouth in 250 cc of water plus 2 cc of normal hydrochloric acid. The curves marked \* represent 75 Gm doses.

Fifty grams of starch was administered to seven, and 75 Gm to two, hospital patients free from alimentary disease or diabetes. The results are shown in chart 1. The blood sugar showed an average increase of 1 mg per hundred cubic centimeters in one-half hour, a decrease of 12 mg in one hour and a decrease of 3 mg in two hours. These results present a striking difference from those obtained in a group of twelve patients to whom 50 Gm of cooked starch was given in the form of mashed potatoes (250 Gm) made up to 500 cc in water, and to which from 6 to 10 cc of 36 per cent hydrochloric acid was added. The experiments with cooked starches will be reported in detail elsewhere, as a technical procedure for studying pancreatic function and intestinal digestion in human subjects. An average increase of 56 mg occurred in one-half hour, of 51 mg in one hour and of 11 mg per hundred cubic centimeters in two hours after the test meal (chart 2).

Another series of tests were performed on seven diabetic patients to whom no insulin had been given for several days preceding the experiments. The results are shown in chart 3. There was an average increase in blood sugar of 6 mg per hundred cubic centimeters in one-

half hour, a decrease of 9 mg in one hour, and a decrease of 14 mg in two and one-half hours after the starch meal. This fall in blood sugar below the initial value is worthy of notice, for it occurred in seven of the nine control cases and in five of the seven diabetic patients. In the normal subjects the fall was negligible, but in the diabetic patients the decrease varied from 14 to 35 mg per hundred cubic centimeters. We do not know whether this fall would have occurred spontaneously or whether it was associated with the starch meal.

A form of carbohydrate which does not raise the blood sugar would be highly desirable in a diabetic regimen, for it would obviate the neces-

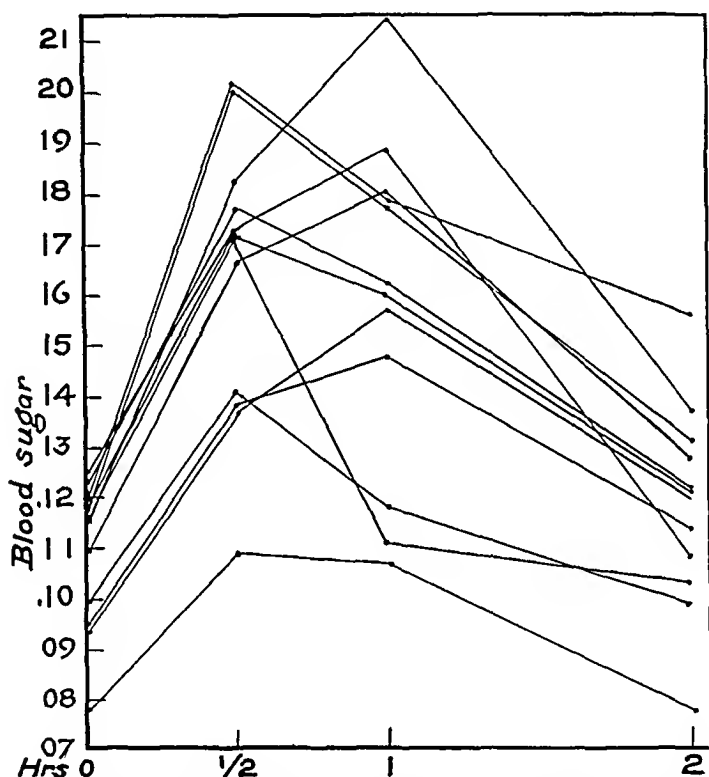


Chart 2—The effect of 50 Gm of cooked starch (250 Gm of potatoes) on the blood sugar of normal adults. Administered by mouth in 500 cc of water plus from 6 to 10 cc of normal hydrochloric acid.

sity of insulin for those patients with moderately severe forms of the disease who develop hyperglycemia and glycosuria after large meals. Further investigation must determine to what extent tolerance can be increased by employing a maintenance diet high in raw starch.

Efforts are being made to employ those foods in which raw starch occurs in an edible form. One of us (R) took a test breakfast of 500 Gm of raw carrots (50 Gm of carbohydrate). They were chewed normally without any attempt to diminish salivary action. Determinations of blood sugar showed before the meal, 0.091 mg per hundred

cubic centimeters, forty-five minutes after, 0.092 mg, one and one-half hours after, 0.086 mg and three hours after, 0.086 mg. Subsequent examination of the stools revealed no appreciable quantities of starch or dextrins. To three diabetic patients a meal of 120 Gm of fresh grated chestnuts was given. Blood sugars during the following three hours showed no elevation. Other edible raw foods, selected because of their

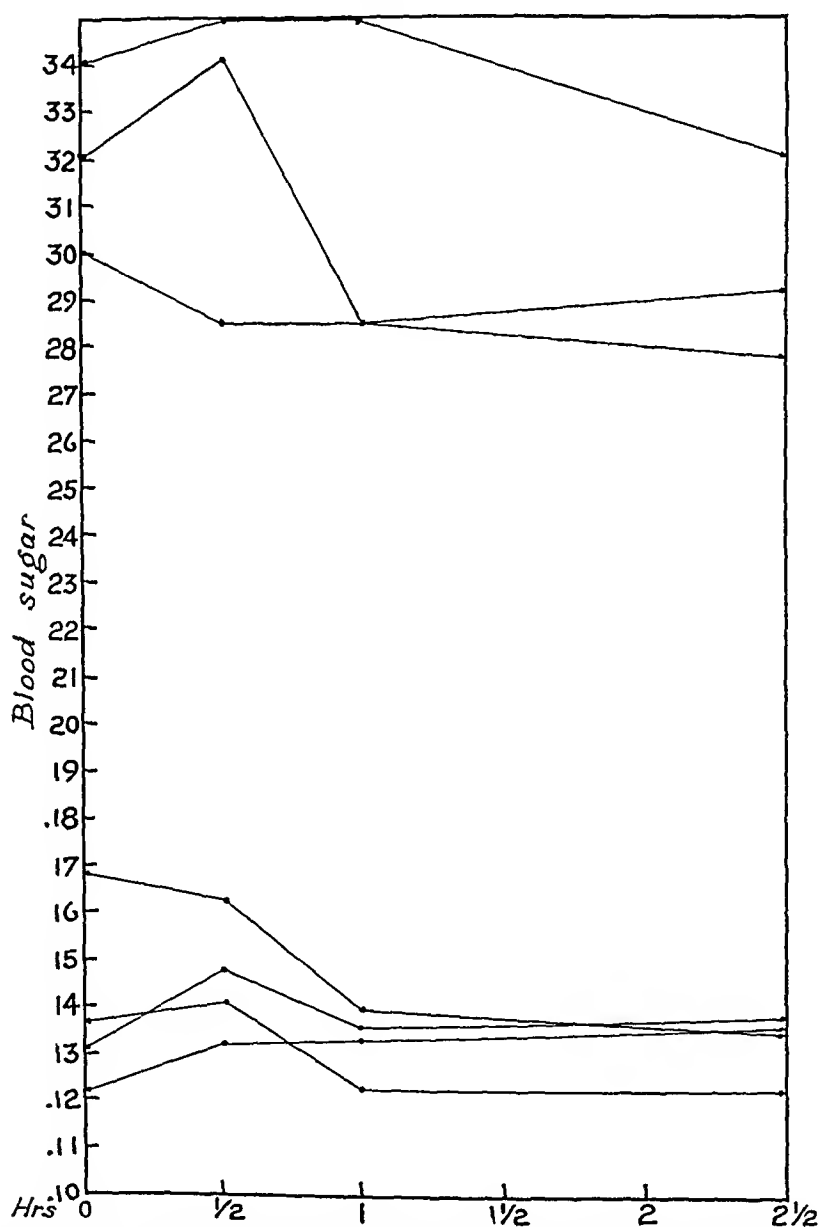


Chart 3—Blood sugar curves following the administration of 50 Gm of raw starch to diabetic patients. Administered by mouth in 250 cc of water plus 2 cc of normal hydrochloric acid.

high caloric value and because the carbohydrates are present principally in the form of starch, such as cocoanut, turnip and onion, are being studied from this point of view. Raw starch itself can be made more palatable by administering it in sweet milk or buttermilk, or in gelatin or frozen puddings.



## COMMENT

In the absence of hyperglycemic effects of raw starches, the question naturally arises as to their digestibility in the alimentary canal. Langworthy<sup>3</sup> kept human subjects on test diets of raw starches for three day periods. The starches were given in a frozen pudding, and examinations of the stools were made to determine their digestibility. Corn, wheat, cassava, rice and taro root starch were completely digested when eaten in amounts up to 250 Gm a day. Potato starch was digested to the extent of 97 per cent when 59 Gm a day was given, and 78 per cent when approximately 200 Gm a day was given. The digestion probably occurs in the distal portion of the alimentary canal, where bacterial action is an accessory to ferment action. The liberation of absorbable sugars would be sufficiently slow so that a hyperglycemia is not produced. This slow absorption does away with the sharp rise in blood sugar that normally occurs following the ingestion of other carbohydrates.

The introduction of this principle into the treatment of diabetic patients is being investigated from the point of view of obviating the use of insulin in mild and moderately severe cases, and to determine whether the total carbohydrate tolerance can be increased by this method of administration.

Another point of interest is the difference in response that occurs between the man and the other animals studied—the dog and the rabbit. It would be expected that the rabbit could rapidly digest raw starch, for this is his native diet, and the amylase in the pancreatic secretion of the rabbit is in a higher concentration than in man. The site of digestion of raw starch in man has been a subject of extensive investigation. Strasburger and his colleagues,<sup>4</sup> as a result of experiments *in vitro*, have recently concluded that digestion takes place in both the small and the large intestine. Our experiments, especially in the light of positive manifestations in animals, prove that no appreciable digestion of raw starch takes place in the upper part of the small intestine of human beings.

The starch that we used (soluble starch) has been treated with strong acid in the process of manufacture and is actually a mixture of starch and higher dextrans. With the use of untreated raw starches, either as such or in the form of uncooked vegetables or nuts, it is possible that the small increases in blood sugar (1 mg in normal subjects and 6 mg in diabetic patients) at the half hour period after administration will not occur.

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3 Langworthy, C. F., and Merrill, A. T. Bull. 1213, U. S. Department of Agriculture, 1924. Langworthy, C. F., and Deuel, H. J. J. Biol. Chem. **51** 251, 1922.

4 Strasburger, J. Arch. f. Verdauungskr. **41** 1, 1927. Strauss. Ibid. **41** 11, 1927. Marx, A. V. Ibid. **41** 180, 1927. Heupke. Ibid. **41** 193, 214, 1927.

The absence of hyperglycemic effects of uncooked starches led us to question whether alimentary hyperglycemia is, in a broad sense, physiologic to man. Krasnjanski<sup>5</sup> and Trimble and Maddock<sup>6</sup> found considerable elevations of blood sugar after each meal, and this was due solely to the carbohydrate content.

The relation of these daily rises in blood sugar to the etiology of diabetes was further suggested by an inquiry into the incidence of diabetes among the Eskimos. These people eat almost no carbohydrate. Dr. H. L. Paddon, for seventeen years in charge of a Labrador hospital

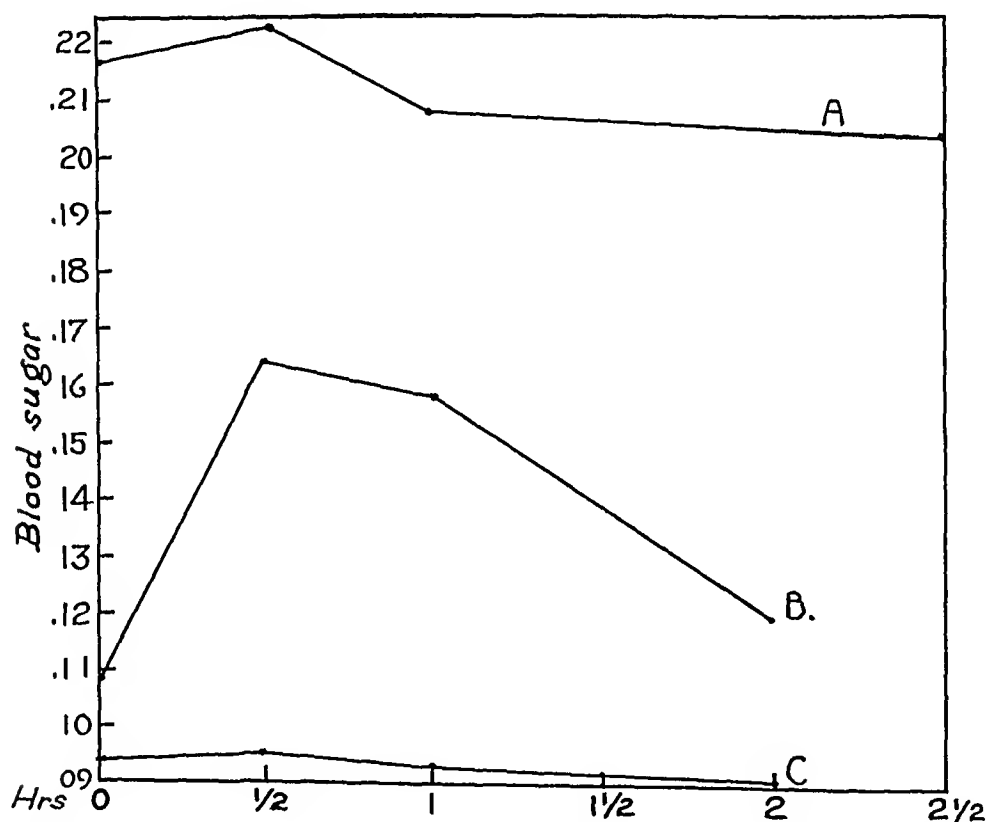


Chart 4—Summary of blood sugar curves following the feeding of starch to human beings. A, 50 Gm of raw starch to seven diabetic patients, B, 50 Gm of cooked starch (250 Gm of potatoes) to twelve normal subjects, C, 50 Gm of raw starch to nine normal subjects.

as a member of Sir Wilfred Grenfell's staff, also Dr. W. A. Thomas and Captain MacMillan, have written me that they have never encountered diabetes in an Eskimo. Dr. A. Bertelson of Copenhagen wrote that a survey of the records shows that among 14,000 Greenland Eskimos who are cared for by ten Danish physicians, diabetes has never been reported to occur.

<sup>5</sup> Krasnjanski, L. M. *Biochem Ztschr* **205** 180, 1929.

<sup>6</sup> Trimble, H. C., and Maddock, S. J. *J Biol Chem* **81** 595, 1929.

## SUMMARY

From 50 to 75 Gm of raw starch administered by mouth to nine normal adults produced the following changes in blood sugar in one-half hour, an average increase of 1 mg per hundred cubic centimeters, in one hour, a decrease of 12 mg, and in two hours, a decrease of 3 mg

Fifty grams of cooked starch (250 Gm of potatoes) given to twelve persons caused the following changes in blood sugar in one-half hour, an average increase of 56 mg, in one hour, an increase of 51 mg, and in two hours, an increase of 11 mg

Fifty grams of uncooked starch was given to seven patients with diabetes of varying severity, the changes in blood sugar were (average) in one-half hour, an increase of 6 mg, in one hour, a decrease of 9 mg, and in two and one-half hours, a decrease of 14 mg

One hundred and twenty grams of uncooked chestnuts were given to three diabetic patients without raising the blood sugar level

# THE AMINO-ACID CONTENT OF THE BLOOD IN HEALTH AND IN DISEASE<sup>\*</sup>

E G SCHMIDT, PH D

BALTIMORE

Among the numerous constituents of the blood stream few are more closely related to many of the fundamental processes of life than the amino-acids. Yet it was only within comparatively recent times (1913) that crystalline amino-acids<sup>1</sup> were actually isolated from the blood stream, and considerable confusion still seems to exist in regard to the amount of amino-acid nitrogen in normal and pathologic blood. Thus in a recent text on biochemistry<sup>2</sup> the statement is found that "in diabetes mellitus there is an accumulation of amino-acids in the blood and a corresponding increased excretion into the urine. Again in nephritis there is an accumulation of amino-acids in the blood." On another page of the same book one finds the statement that "amino-nitrogen rarely rises in the blood. Even during severe nephritis there is no characteristic increase in amino-nitrogen." In a recent book on blood chemistry,<sup>3</sup> the author said that "a definite rise in the amino-acid content of the blood appears only to have been recognized in acute yellow atrophy," whereas another author on the same subject<sup>4</sup> stated that "they have been found to be increased in nephritis but the clinical value of the determination is uncertain." Other writers of textbooks also indicate that the amino-acid nitrogen is increased in severe nephritis.<sup>5</sup> However, in their early work on the metabolism of the amino-acids, Folin and Berglund<sup>6</sup> pointed

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<sup>\*</sup> Submitted for publication, Jan 23, 1929

<sup>\*</sup> From the Biochemical Laboratory of Mercy Hospital and the Department of Biological Chemistry of the University of Maryland School of Medicine

1 Abel, J J, Rowntree, L G, and Turner, B B. *Tr Am A Phys*, May 6, 1913, p 4

2 Morse, W. *Applied Biochemistry*, ed 2, Philadelphia, 1927, pp 542 and 837

3 De Wesselow, O L V. *The Chemistry of the Blood in Clinical Medicine*, New York, 1924, p 24

4 Kilduffe, R A. *The Clinical Interpretation of Blood Chemistry*, Philadelphia, Lea & Febiger, 1927, p 96

5 Hawk, P B, and Bergeim, O. *Practical Physiological Chemistry*, ed 9, Philadelphia, 1927, p 357. Rehfuess, M E. *Diagnosis and Treatment of Diseases of the Stomach*, Philadelphia, W B Saunders Company, 1927, p 1086. Myers, V C. *Practical Chemical Analysis of the Blood*, ed 2, St Louis, C V Mosby Company, 1924, p 32

6 Folin, O. *Laboratory Manual of Biological Chemistry*, ed 4, New York, D Appleton & Company, 1925, p 291. Berglund, H. *Nitrogen Retention in Chronic Intestinal Nephritis*, *J A M A* 79 1375 (Oct 21) 1922

out that the deaminization process is so fundamental that few conditions will be found in which the amino-nitrogen varies much from the normal. Papers in the current literature are equally as confusing as the statements in many of the textbooks and will be discussed in connection with the data from the laboratory.

This situation is due, probably, to the variety of methods which have been utilized for the determination of the amino-acids of the blood, viz., the "ninhydrin" reaction of Abderhalden, the Sorenson titration method, the gasometric method of van Slyke, the colorimetric reaction of Folin, etc., and the various methods which have been used for the preparation of the protein-free filtrates. Hence the exact amount of amino-acid nitrogen in an individual specimen will depend on the nature of the method that was used for the analysis. While this fact, however, may not vitiate completely the conclusions drawn from an individual paper, the data would hardly be comparable with those of another work in which a different analytic procedure was utilized.

The colorimetric method of Folin<sup>7</sup> in which sodium beta-naphthoquinone 4-sulphonate is used as the color reagent avoids many of the errors and difficulties inherent in the other methods for the determination of the amino-acid nitrogen of the blood, and as the method is adaptable to hospital routine it was used exclusively in this work. During the last two years, about 500 determinations have been made of the amino-acid nitrogen of the blood taken during fasting from patients with a considerable diversity of disease. The diagnoses taken from the charts of the patients were primarily clinical, although a few were confirmed by postmortem observations, and especial attention was given to those conditions in which uncertainty seems to exist as to the actual amino-acid content of the blood.

The amino-acid nitrogen of the blood specimens representing a considerable variety of diseases was found to be remarkably constant and showed but little variation from the normal range as found in healthy adults. In many diseases, such as uremia, diabetes, pneumonia, pernicious anemia, hepatic insufficiency, etc., in which the amino-acid nitrogen is reported to be appreciably elevated, normal results were obtained in all cases. Pathologic variations in the content of amino-acid nitrogen, among the cases examined in the laboratory, were found only in leukemia and acute yellow atrophy of the liver. In addition, it can be stated definitely from a survey of the literature that the amino-acids are also increased in polycythemia vera, and as a result of such hepatic poisons as hydrazine, synthalin, chloroform, etc., while large doses of insulin produce a decrease in the amino-acid nitrogen of the blood.

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<sup>7</sup> Folin, O. J. Biol. Chem. **51** 377, 1922

## EXPERIMENTAL METHODS

Folin's colorimetric method was used for the determination of the amino-acid nitrogen of the blood, and all precautionary measures were taken to insure accuracy of results. In order to avoid any postprandial hyperamino-acidemia, the blood specimens were collected in the morning before breakfast and after a twelve hour fast in tubes containing about 10 mg of lithium oxalate. The protein-free filtrates were immediately prepared according to Haden's<sup>8</sup> modification of the original Folin-Wu technic, in which twelve hundredth-normal sulphuric acid is used instead of the two-third normal acid. During the last few years, several thousand filtrates have been prepared in the laboratory by this method with excellent results, the filtrates always come through rapidly and are invariably clear and colorless. The filtrates, of course, were used for the other chemical analyses also. Ten cubic centimeters of the filtrate was used for each determination, and two amino-acid standards were prepared and matched with each other in the colorimeter in each run. If the standards checked with each other they were read against the unknown preparations.

## REAGENTS

The stock amino-acid solution containing 0.1 mg of amino-acid nitrogen per cubic centimeter was prepared by dissolving 0.1339 Gm of glycine (Pfanstiehl) in tenth-normal hydrochloric acid containing 0.5 Gm of sodium benzoate, and the solution was then diluted to 250 cc with tenth-normal hydrochloric acid. The standard amino-acid solution was prepared by diluting 175 cc of the stock solution to 250 cc with the tenth-normal hydrochloric acid. This standard has been compared colorimetrically and found to check closely with the standard glycine solutions in use in two other laboratories. The special sodium carbonate solution was prepared by diluting 50 cc of a saturated solution with distilled water until 85 cc were exactly equivalent to 20 cc of tenth-normal hydrochloric acid, with methyl red as the indicator. The acetic acid-acetate and sodium thiosulphate solutions were also prepared according to the directions of Folin.<sup>7</sup> The sodium naphthoquinone 4-sulphonate of various manufacturers was found not to be of uniform quality, and the specified amount of one particular brand would hardly take care of the amino-acid nitrogen found in 10 cc of a protein-free filtrate. However, a satisfactory product was secured from the Eastman Kodak Company and was tested out in the following manner. A series of amino-acid standards were prepared by diluting aliquot quantities of the stock solution to various volumes with tenth-normal hydrochloric acid in such a manner that 1 cc of each of the diluted glycine solutions contained the amount of amino-acid nitrogen as given in the first column of table 1. The figures, however, have been multiplied by 100 in order to make them comparable with the figures obtained from blood filtrates where the calculations are based on milligrams of amino-acid nitrogen per hundred cubic centimeters of blood. The amino-acid nitrogen in each glycine solution was determined in the usual manner and compared with the regular standard. Then a series of determinations were made in which various amounts of the freshly prepared beta-naphthoquinone solution was added to the different glycine solutions and then matched in the colorimeter against the usual amino-acid standard. The data are given in table 1 and show that each cubic centimeter of the 0.5 per cent beta-naphthoquinone solution takes care of from about 0.08 to 0.1 mg of amino-acid nitrogen. Thus, if the blood is suspected to be high in amino-acids the filtrate should

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<sup>8</sup> Haden R. L. J Biol Chem 56 469, 1923

be diluted, or more of the quinone reagent should be used in the determination. By carefully following the directions of Folin in every detail, I have never encountered any difficulties with the method, and uniformly satisfactory results were always obtained.

## RESULTS

In regard to the average amount of amino-acid nitrogen in the blood of healthy adults, various figures have been reported, the inconsistencies

TABLE 1—*The Effect of Varying the Amounts of Amino-Acid Nitrogen and the Naphthoquinone Reagent*

Amino Acid Nitrogen Added, Mg*	1 Cc Naphthoquinone			2 Cc Naphthoquinone			3 Cc Naphthoquinone		
	Colorimeter Reading, Mm	Amino-Acid Nitrogen Found, Mg*	Difference, Mg*	Colorimeter Reading, Mm	Amino Acid Nitrogen Found, Mg*	Difference, Mg*	Colorimeter Reading, Mm	Amino Acid Nitrogen Found, Mg*	Difference, Mg*
42.0	13.0	10.8	-31.2	6.5	21.5	-20.5	4.7	29.8	-12.2
31.5	13.0	10.8	-20.7	6.5	21.5	-10.0	5.3	26.4	-5.1
21.0	13.5	10.4	-10.6	6.6	21.2	+0.2	6.8	20.6	-0.6
14.0	13.5	10.4	-3.6	10.2	13.7	+0.3	10.0	14.0	0.0
10.7	16.0	8.8	-1.9	13.0	10.8	-0.1	13.0	10.8	+0.1
8.4	16.1	8.7	+0.3	15.5	9.0	+0.6	16.0	8.8	+0.4
7.0	22.0	6.4	-0.6	20.0	7.0	0.0	20.2	6.9	-0.1
6.0	24.0	5.8	-0.2	22.5	6.2	+0.2	24.0	5.8	-0.2
5.0	29.0	4.8	-0.2	28.0	5.0	0.0	27.0	5.2	+0.2
4.0	33.0	4.2	+0.2	32.5	4.3	+0.3	33.0	4.2	+0.2

\* Each figure has been multiplied by 100

TABLE 2—*Amino-Acid Nitrogen Content of Normal Blood*

Author of Report	Mg per 100 Cc Blood		
	Minimum	Maximum	Average
Folin, O, and Berglund, H, 12 young men <sup>a</sup>	5.7	7.8	6.4
Greene, C H Sandford, K, and Ross, H (J Biol Chem 53 845, 1924) 20 normal persons	5.2	7.2	6.37
Fownweather, F S, and Gordon, J (Brit J Exper Path 8 93, 1927) 15 normal cases	4.9	8.1	6.46
McClure, C W, and Huntsinger, M E (J Biol Chem 74 1, 1928) 15 normal persons	4.8	7.5	6.6
Hoeffel, G N, and Moriarty, M E (Am J Dis Child 27 64 [Jan] 1924) 14 normal adults	6.4	8.1	7.04
Wowsi, M, and Gelbird, J (Ztschr f d ges exper Med 51 518, 1926) 30 normal persons	5.3	8.0	
Schmidt, E G (this paper) 25 adults	1.8	7.8	6.3

are probably due to the different procedures which were used for the analyses. The more reliable reports of the various investigators who have utilized the Folin colorimetric method for the determination of the amino-acid nitrogen of the blood have been collected in table 2. The general average is thus seen to be from 6.3 to 6.5 mg of amino-acid nitrogen per hundred cubic centimeters of blood. The results of the analysis of the blood of twenty-five normal adults and adults with minor surgical conditions were found to average 6.3 mg and to range from 4.8

to 78 mg of amino-acid nitrogen per hundred cubic centimeters of blood, and are thus in good agreement with most of the figures in table 2

The results of the analysis of the pathologic specimens of blood are given in table 3 and include the number of cases of each disease and

TABLE 3—*The Amino-Acid Nitrogen Content of the Blood in Various Diseases*

Diagnoses	Mg per 100 Ce			
	Number of Cases	Minimum	Maximum	Average
Appendicitis (chronic and acute)	7	58	70	63
Alcoholism (chronic and acute)	9	56	67	62
Gastric ulcer	3	50	67	64
Intestinal obstruction	7	64	67	66
Gastritis	2	65	65	65
Achlorhydria	2	55	57	56
Gastroparesis	1			61
Chemical poisoning (lead, arsenic, carbon monoxide, etc)	5	55	67	60
Colitis	2	60	64	62
Malnutrition	3	64	65	64
Adhesions	4	58	72	66
Pneumonia (lobar and bronchopneumonia)	17	47	80	61
Grip, laryngitis, bronchitis, etc	7	60	66	63
Rheumatic cardiovascular disease	2	57	59	58
Syphilitic cardiovascular disease	2	61	68	65
Arteriosclerotic cardiovascular disease	20	50	83	65
Hypertensive cardiovascular disease	10	56	74	66
Hypertension (essential and paroxysmal)	14	56	74	64
Hypotension	2	61	61	61
Neurocirculatory asthenia	2	58	61	60
Aneurysm of aorta	2	64	66	65
Cerebral accidents (hemorrhages, thrombosis, etc)	11	56	76	67
Angina pectoris	2	69	80	75
Myocardial degeneration with cardiac decompensation	8	41	69	58
Gynecologic and obstetric conditions as pregnancy, toxemia, cysts, fibroids, pyelitis salpingitis, etc	40	40	72	60
Neurologic conditions	18	50	67	62
Benign hypertrophy of prostate	9	56	70	65
Peritonitis	4	52	70	63
Hernia (various types)	9	58	70	64
Syphilis (various types)	8	58	68	62
Neoplasms (benign and malignant)	10	41	64	60
Gallbladder diseases	8	55	70	60
Arthritis (various types)	4	58	63	61
Serum reaction	1			70
Neuritis	1			49
Gout	4	50	70	60
Retinitis pigmentosa	1			82
Hemolytic jaundice	1			82
Nephrosis	3	55	57	56
Hemiplegia	1			68
Thyroid dysfunction	6	57	67	60
Anemia (secondary and pernicious)	10	50	80	64
Cirrhosis of the liver	5	60	78	72
Diabetes mellitus—blood sugar 44 (insulin shock)	1			45
Diabetes mellitus—blood sugar 100 to 150	22	52	70	63
Diabetes mellitus—blood sugar 150 to 200	25	45	69	50
Diabetes mellitus—blood sugar 200 to 250	15	47	69	62
Diabetes mellitus—blood sugar 250 to 300	15	58	68	63
Diabetes mellitus—blood sugar 300 to 400	6	61	76	66
Diabetes mellitus—blood sugar 400 to 600	2	64	66	65
Tuberculous meningitis	1			69
Renal diseases (from table 5)	35	45	88	63
Miscellaneous and outpatients	40	58	72	63
Average of 449 determinations	—	—	—	63
Normal persons and those undergoing minor operations	25	48	78	63

the minimal, maximal and average content of amino-acid nitrogen. In spite of the wide variety of diseases represented in the specimens subjected to examination, the blood was found to be remarkably constant in amino-acids and did not deviate appreciably from the normal range found in healthy adults. The figures were found to range from 4 to 83 mg,



with an average amino-acid nitrogen of 6.3 mg, the same average as was established for normal blood. The only case in which the amino-acid appreciably exceeded 8 mg was one of arteriolar nephritis (table 5, no. 14) which showed 8.8 mg of amino-acid per hundred cubic centimeters of blood, the blood having been taken just prior to death. This value may be explained in the light of the recent work of Becker,<sup>9</sup> who pointed out that the amino-acids of the blood begin to increase just prior to death, and that the rise is rapid soon after life ceases. However, most of the cases in which the amino-acid was slightly in excess of 8 mg (from 8 to 8.3 mg) were found to yield normal values on reexamination within a few days. The distribution of amino-acid nitrogen and frequency of occurrence of the various values are given in table 4 and indicate that 180 determinations, or 40.09 per cent, occurred between 6 and 6.4 mg, and therefore 6.3 mg is close to the probable average amino-acid nitrogen content of the blood. The results in regard

TABLE 4—*The Distribution of Amino-Acid Nitrogen and Frequency of Occurrence*

Amino Acid Nitrogen, Mg per 100 Cc	Number of Occurrences	Per Cent
4.0 to 4.4	2	0.44
4.5 to 4.9	13	2.89
5.0 to 5.4	40	8.89
5.5 to 5.9	70	15.59
6.0 to 6.4	180	40.09
6.5 to 6.9	84	18.71
7.0 to 7.4	39	8.63
7.5 to 7.9	11	2.45
8.0 to 8.4	8	1.78
8.5 to 8.8	1	0.22

to certain diseases merit further discussion and will be taken up in connection with the reports of other workers.

*Results in Certain Diseases*—Nephritis. As previously pointed out, the rather scanty literature on the subject of the possible retention of amino-acids in renal disease is full of conflicting statements. The earlier work was carried out with the gasometric method of van Slyke on filtrates which had been deproteinized in a variety of ways. Thus Bock<sup>10</sup> found that among the numerous diseases in which the amino-acids were increased the most pronounced variations from the normal occurred in nephritis, and his results are quoted in most texts on biochemistry and chemical pathology. Okada and Hayashi<sup>11</sup> confirmed the results of Bock on patients with severe uremia, and they also found increased amino-acids in the blood of dogs after ligating the ureters or

<sup>9</sup> Becker, E., and Herrman, E. *Munchen med Wchnschr* **72** 1069 and 2178, 1925.

<sup>10</sup> Bock, J. C. *J Biol Chem* **28** 357, 1916, *ibid* **29** 191, 1916.

<sup>11</sup> Okada, S., and Hayashi, T. *J Biol Chem* **51** 121, 1922.

extirpating the kidneys Blau,<sup>12</sup> Desqueyroux,<sup>13</sup> Hulse and Strauss<sup>14</sup> and others, also found increased amino-acids in advanced renal disease, whereas Losee and van Slyke<sup>15</sup> and Morse<sup>16</sup> found no marked deviations from the normal in pre-eclamptic toxemia, eclampsia, nephritic toxemia and similar conditions. In general, the results secured with the colorimetric method of Folin yielded normal results in most diseases. Thus Folin and Beiglund,<sup>6</sup> in a small series of cases, found that the amino-acids did not parallel the retention of urea, while Greene, Sandiford and Ross<sup>17</sup> found that "there is no significant departure from the normal and no apparent correlation between the amino-acids and degree of renal insufficiency." Feinblatt and Shapiro<sup>18</sup> reported that "while in an individual instance urea retention is apt to be accompanied by hyperamino-acidemia, this association is just as often completely lacking" and that, as a rule, normal values are usually obtained. Bandler and Killian<sup>19</sup> reported a case of cancer of the bladder in which the amino-acid nitrogen showed a terminal rise to 12 mg. Looney<sup>20</sup> found, in an individual case of mercuric chloride poisoning with retention and anuria, that the amino-acids did not increase until shortly before death. However, in a recent investigation of the rôle of the liver in amino-acid metabolism, Wowski and Gelbird<sup>21</sup> noted an increase of amino-acids in the blood in cases of cancer (especially of the stomach and liver), syphilis, acute yellow atrophy of the liver and severe hepatitis as well as in leukemia, uremia, pneumonia, and other diseases.

In table 5 is listed a series of blood chemistry studies of thirty-five patients with various types and in diverse stages of renal disease. The blood urea values ranged from 19 to 610 mg, and the creatinine from 1.5 to 15 mg per hundred cubic centimeters of blood. The average amino-acid nitrogen of the thirty-five patients was found to be 6.3 mg, exactly normal, with a minimum of 4.5 and a maximum of 8.8 mg, therefore, regardless of the degree of renal damage, the amino-acid nitrogen content of the blood showed no appreciable departure from the normal values. In only one case did the amino-acid nitrogen exceed 8 mg (no. 14), the blood for that determination, however, was taken just before death. In connection with such conditions as intestinal

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12 Blau, N. F. *J. Biol. Chem.* **56** 861 and 867, 1923.

13 Desqueyroux, J. *Ann. de med.* **13** 20 (Jan.) 1923.

14 Hulse, W., and Strauss, H. *Ztschr. f. d. ges. exper. Med.* **39** 442, 1924.

15 Losee, J. R., and van Slyke, D. D. *Am. J. M. Sc.* **158** 94, 1917.

16 Morse, A. *Bull. Johns Hopkins Hosp.* **28** 199, 1917.

17 Greene, C. H., Sandiford, K., and Ross, H. *J. Biol. Chem.* **53** 845, 1924.

18 Feinblatt, H. M., and Shapiro, L. *Amino-Acid Content of Blood in Various Pathologic Conditions*, *Arch. Int. Med.* **34** 690 (Nov.) 1924.

19 Bandler, C. G., and Killian, J. A. *J. Urol.* **19** 1, 1928.

20 Looney, J. M. *J. Biol. Chem.* **70** 513, 1926.

21 Wowski, M., and Gelbird, J. *Ztschr. f. d. ges. exper. Med.* **51** 518, 1926.

obstruction, pneumonia, etc., in which the urea content is considerably elevated, no increase in amino-acids was noted

**Pernicious Anemia** Several investigators, especially Gettler and Lindeman<sup>22</sup> and Gorchkoff, Grigorieff and Koutoursky<sup>23</sup> have reported increases in the amino-acid content of the blood in pernicious anemia, whereas others<sup>24</sup> found normal values. Table 3 includes ten cases of anemia of various types, and the amino-acid nitrogen was found to average 6.4 mg. with no deviations from the normal range.

TABLE 5—*The Amino-Acid Nitrogen Content of Blood in Renal Disease*

	Diagnosis	Blood Chemistry		
		Urea Mg	Creatinine Mg	Amino Acid Nitrogen Mg
1	Acute nephrosis, mercuric chloride poisoning	610	8.4	61
2	Chronic diffuse glomerular nephritis	585	6.4	7.4
3	Chronic interstitial nephritis	575	8.4	61
4	Pyonephrosis	565	8.0	7.8
5	Pyonephrosis	555	12.0	67
6	Pyonephrosis	485	9.0	47
7	Acute nephrosis, mercuric chloride poisoning	480	9.8	56
8	Acute nephrosis, mercuric chloride poisoning	425	6.0	67
9	Chronic interstitial nephritis	415	10.0	52
10	Pyonephrosis	405	5.6	5.0
11	Chronic diffuse glomerular nephritis	405	6.4	6.4
12	Acute nephrosis, mercuric chloride poisoning	395	9.4	7.4
13	Acute nephritis	385	9.2	5.8
14	Arteriolar nephritis	340	8.0	8.8
15	Pyonephrosis	333	12.0	5.4
16	Acute nephrosis, mercuric chloride poisoning	320	7.0	7.0
17	Chronic nephritis	277	15.0	5.1
18	Chronic diffuse glomerular nephritis	247	6.4	6.4
19	Chronic diffuse glomerular nephritis	215	7.0	6.3
20	Chronic diffuse glomerular nephritis	215	6.4	6.1
21	Bilateral pyelonephritis (advanced)	200	3.4	6.3
22	Chronic diffuse glomerular nephritis	200	10.0	7.0
23	Acute nephrosis, mercuric chloride poisoning	180	5.0	6.1
24	Chronic interstitial nephritis	166	2.2	6.2
25	Chronic diffuse glomerular nephritis	166	4.8	5.4
26	Chronic diffuse glomerular nephritis	150	3.8	4.5
27	Bilateral pyonephrosis	150	2.6	6.4
28	Acute nephritis	149	1.6	7.7
29	Chronic arteriolar nephritis	104	1.9	7.4
30	Acute focal glomerular nephritis	98	2.4	6.4
31	Acute focal glomerular nephritis	94	2.8	7.2
32	Chronic arteriolar nephritis	73	1.9	6.4
33	Chronic arteriolar nephritis	61	1.5	6.0
34	Chronic interstitial nephritis	40	1.4	6.3
35	Chronic interstitial nephritis	19	1.5	5.8
Average				6.3

**Diabetes Mellitus** In diabetes mellitus a number of investigators, including Labbé and Violle,<sup>25</sup> Galambos and Tausz,<sup>26</sup> Wolpe,<sup>27</sup>

22 Gettler, A. O., and Lindeman, E. Blood Chemistry of Pernicious Anemia, Arch Int Med **26** 453 (Oct) 1920

23 Gorchkoff, M., Grigorieff, W., and Koutoursky, A. Compt rend Soc de biol **76** 454, 1914

24 Greene, Sandiford and Ross (footnote 17) Feinblatt and Shapiro (footnote 18)

25 Labbé, H., and Violle, K. Compt rend Acad d sc **154** 73, 1912

26 Galambos, A., and Tausz, B. Ztschr f klin Med **77** 14, 1913, ibid **80** 381, 1914

27 Wolpe, G. Munchen med Wchnschr **71** 363, 1924

Desqueyroux<sup>13</sup> and others, found increased amino-acids with the van Slyke method, whereas Greene, Sandiford and Ross,<sup>17</sup> Feinblatt and Shapiro,<sup>18</sup> von Falkenhausen<sup>28</sup> and others found no increase in the amino-acids with the Folin method. Table 3 includes the amino-acid nitrogen content of eighty-five diabetic patients in various stages of insulin therapy with blood sugar values ranging from 100 to 600 mg per hundred cubic centimeters of blood. The amino-acid nitrogen of these specimens of blood from diabetic patients was found to range from 4.5 to 7.6 mg with an average of 6.3 mg for the eighty-five determinations, and all were well within the normal range. This series also includes a young diabetic child in coma from insulin shock whose blood sugar was 44 mg and the corresponding amino-acid nitrogen 4.5 mg, which might indicate that an overdose of insulin produces a decrease in the amino-acids of the blood. This observation would be in keeping with the experiments of Luck, Morrison and Wilbur<sup>29</sup> who demonstrated that subconvulsive doses of insulin lowered the amino-acid content of the blood of rabbits, rats and human beings, the maximum decrease was from 2.5 to 3 mg. Greene, Sandiford and Ross<sup>17</sup> stated that insulin has no effect on the amino-acids, however, Tashiro,<sup>30</sup> Wiechmann,<sup>31</sup> Wolpe<sup>27</sup> and others agreed that insulin produces a reduction in the amino-acids of the blood. On the other hand, parenteral administrations of such antidiabetic substances as synthalin<sup>32</sup> and other insulin substitutes<sup>33</sup> have been found to produce an increase in the amino-acids of the blood, which was attributed to injury to the liver as exhibited by a decreased ability to deaminate injected glycine. In this connection Lewis and Izume<sup>34</sup> found that the subcutaneous administration of hydrazine sulphate to fasting rabbits often produced fatty degeneration of the liver as shown by a marked rise in the amino-acids of the blood, while Marshall and Rowntree<sup>35</sup> found that phosphorus and especially chloroform also produced an amino-acidemia and a decrease in blood urea.

**Hepatic Insufficiency** My views of the metabolism of the amino-acids primarily center around the functions of the liver and rest largely

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28 Von Falkenhausen, M. F. *Arch f exper Path u Pharmacol* **103** 322, 1924

29 Luck, J. M., Morrison, G., and Wilbur, L. *J Biol Chem* **77** 151, 1928

30 Tashiro, K. *Tohoku, J Exper Med* **7** 221, 1926

31 Wiechmann, E., and Dominick, M. *Arch f klin Med* **153** 1, 1926

32 Blatherwick, N. R., Sahyun, M., and Hill, E. *J Biol Chem* **75** 671, 1927

33 Bischoff, F., Blatherwick, N. R., and Sahyun, M. *J Biol Chem* **77** 467, 1928

34 Lewis, H. B., and Izume, S. *J Biol Chem* **71** 33, 1926

35 Marshall, E. K., Jr., and Rowntree, L. G. *J Exper Med* **22** 333, 1915

on the evidence presented by the work of van Slyke,<sup>36</sup> Folin<sup>37</sup> and Mann<sup>38</sup> and others. On complete removal of the liver of dogs, Mann and his collaborators demonstrated that there resulted a complete cessation of deamination and a resultant increase in the amino-acid content of the blood. Evidence has been presented to show that in diseases of hepatic origin there is an increased content of amino-acids,<sup>39</sup> but Greene, Sandiford and Ross<sup>17</sup> found no increase in a number of cases of cirrhosis or chronic hepatitis, and the limited data in table 3 are in conformity with the latter statement. However, Wowski and Gelbird,<sup>21</sup> who also used the method of Folin, found that the amino-acids were increased in syphilitic and arsenical hepatitis and especially in primary cancer of the liver and in acute yellow atrophy, whereas normal values were secured in infectious and toxic jaundice. The fact is well known that in acute yellow atrophy there is found a marked increase in the amino-acids of the blood and urine.<sup>40</sup> In the single case of acute yellow atrophy of the liver

TABLE 6—*Amino-Acid Nitrogen Content in Leukemia*

Number	Date	Amino Acid Nitrogen, Mg	Leukocyte Count
1	3/ 1/28	10.3	540,000
2	3/ 8/28	9.2	76,800
3	6/20/28	8.0	230,000
4	11/21/28	4.9	7,900
4	11/22/28	5.4	5,900
4	11/23/28	7.6	59,000
5	12/27/28	7.2	80,000

reported in this paper the following laboratory observations per hundred cubic centimeters of blood were secured: amino-acid nitrogen, 16.5 mg, urea, 29 mg, nonprotein nitrogen, 57 mg, sugar, 50 mg, and sodium chloride, 380 mg. The van den Bergh reaction was prompt direct positive with 22 mg of bilirubin per hundred cubic centimeters of serum, and the icterus index was 200. These figures are typical of acute yellow atrophy.

36 Van Slyke, D. D. The Harvey Lectures, 1915-1916, vol 11, p 146

37 Folin, O. *Physiol Rev* **2** 460, 1922

38 Mann, F. C. *Medicine* **6** 419, 1927

39 Rowntree, L. G., Marshall, E. K., and Chesney, A. M. *Tr Am A Phys* **29** 586, 1914

40 Wolpe (footnote 27) Feigle, J., and Luce, H. *Biochem Ztschr* **79** 162, 1917  
 Roman, B. *Acute Yellow Atrophy of Liver*, *Arch Path* **4** 399 (Sept) 1927  
 Stadie, W. C., and van Slyke, D. D. *Effect of Acute Yellow Atrophy on Metabolism and on Composition of the Liver*, *Arch Int Med* **25** 693 (June) 1920  
 Tileston, W., and Comfort, C. W. *The Total Nonprotein Nitrogen and the Urea of the Blood in Health and in Disease, as Estimated by Folin's Methods*, *ibid* **14** 620 (Nov) 1914

**Polycythemia Vera (Erythremia)** Greene and Conner <sup>41</sup> stated that true polycythemia is the converse of anemia in that it is characterized by a persistent increase in the red blood corpuscles with resultant plethora, and they found that the amino-acids are moderately (from 8 to 14.3 mg) increased in the blood. Luck <sup>42</sup> also reported that the amino-acids are increased in polycythemia. No cases of polycythemia were encountered while this work was in progress.

**Leukemia** In leukemia, particularly of the myelogenous type, the blood has been found to contain a moderate increase of amino-acid nitrogen <sup>43</sup>. It is said that in general the concentration of amino-acids parallels approximately the leukocyte count, and that there is some, but not necessarily a proportionate, increase in the basal metabolism <sup>44</sup>. While this work was in progress, five cases of lymphatic leukemia of various types were encountered, and the following data indicate that a small increase in amino-acid nitrogen is frequently found if associated with a high leukocyte count.

Certain phases of this work are still being continued.

#### SUMMARY

1 The amino-acid nitrogen content of normal adult blood, as determined by the Folin colorimetric method with sodium beta-naphthoquinone 4-sulphonate, was found to average 6.3 mg and to range from 4.8 to 7.8 mg per hundred cubic centimeters of blood.

2 The analysis of almost 500 specimens of blood representing a considerable diversity of disease proved that the concentration of amino-acids remains remarkably constant. The values range from 4 to 8.3 mg with an average of 6.3 mg per hundred cubic centimeters of blood.

3 The amino-acid nitrogen content of the blood was found to be frequently moderately increased in leukemia and greatly elevated in acute yellow atrophy of the liver. The amino-acids are also increased (no data in this paper) in polycythemia vera, and as a result of the administration of such hepatic poisons as hydrazine sulphate, synthalin, chloroform and phosphorus.

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41 Greene, C. H., and Conner, H. M. Diseases of the Liver. Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System, *Arch. Int. Med.* **38**, 167 (Aug.) 1920.

42 Luck, J. M. *J. Biol. Chem.* **77**, 13, 1928.

43 Okada and Hayashi (footnote 11). Martin, C. L., Denis, W., and Aldrich, M. *Am. J. M. Sc.* **160**, 223, 1920.

44 Sandiford, K., Boothby, M., and Giffen, H. *J. Biol. Chem.* **55**, 23, 1923.

# FAILURE OF A DIABETIC PATIENT TO UTILIZE DRIED ARTICHOKE POWDER \*

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For a number of years the use of artichokes has been of interest in the treatment of diabetic patients and has been discussed frequently in numerous papers. Root and Baker<sup>1</sup> fed twenty-five diabetic patients Jerusalem artichokes in addition to their regular diet. Occasionally, artichokes, a 15 per cent vegetable, were substituted for a 5 per cent vegetable. In some cases the artichokes were taken daily, in others on alternate days, and in one instance, only once a week. The average amount of uncooked artichokes taken per day amounted to 130 Gm. If we interpret their table correctly, seventeen patients increased their carbohydrate tolerance from 51 to 59 Gm exclusive of approximately from 19 to 20 Gm of carbohydrate, which was added as artichoke. The intake level for fat was slightly improved. In short, the calory intake was successfully increased from 1,353 to 1,501, or 148 calories, of which about 112 calories came from the artichokes. We might conclude that an additional tolerance of the levulose sugars over the dextrose sugars, amounting to approximately 30 Gm, is established. It must be mentioned, however, that the dosage of insulin was increased by 3 units per day. Additional evidence along this line was obtained when 100 Gm of artichokes, replacing 15 Gm of dextrose sugars, rendered the urine sugar-free. Another patient replaced the 5 per cent vegetable with artichokes in equivalent amount. This increased her carbohydrate intake by 10 Gm, and she became sugar-free.

Carpenter and Root<sup>2</sup> reported that when carbohydrate was fed in a comparative way, with the use of artichokes and potatoes, at a level of 205 Gm of carbohydrate (of which 110 Gm came from the two sources mentioned), about 10.5 Gm of sugar was found in the urine of patients on the potato diet but none in that of those on the artichoke diet.

A reasonable interpretation of these experiments would lead us to conclude that there is a slightly greater tolerance for the levulose deriva-

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\* Submitted for publication, March 20, 1929.

1 Root, H. F., and Baker, M. L. Inulin and Artichokes in the Treatment of Diabetes, *Arch. Int. Med.* **36** 125 (July) 1925.

2 Carpenter, T. M., and Root, H. F. Utilization of Jerusalem Artichokes by Patient with Diabetes, *Arch. Int. Med.* **42** 64 (July) 1928.

tives in this form than for the usual dextrose carbohydrates and that it might amount to as much as 30 Gm per day

Joslin<sup>3</sup> summarized as follows "Twelve patients took an average of 92 grams of artichokes in addition to their regular diets without increasing glycosuria already present or producing glycosuria in patients previously sugar free. The average increase in carbohydrate was thus about 13 grams"

Our object in the work recorded in this paper was to study the qualitative aspect of this question with a diabetic patient who was not receiving insulin. In brief, we carefully determined the carbohydrate tolerance in the usual manner. We then dropped the carbohydrate intake just below the known tolerance and superimposed dried artichoke powder in weighed amounts and again determined the tolerance. We conclude that the tolerance is not appreciably increased by the artichokes.

#### REPORT OF CASE

J. C. P., a man, aged 22, unmarried, employed as a bank clerk, presented an unimportant past and family history. In August, 1927, he felt "run down" and received a tonic from his family physician. No urinary symptoms were noted at this time, and within a month he felt entirely well. In March, 1928, he began to feel exhausted during the morning and had not felt well since that time. In October, 1928, the urinary symptoms, pollakiuria, polyuria and polydipsia were first noted. Polyphagia accompanied these symptoms, and about the first of November the patient noticed a dry skin and dry mouth.

*Examination*—Examination on Nov. 12, 1928, showed a blood sugar content of 254 mg per hundred cubic centimeters and a urine sugar content of 6 per cent. The urine was negative for diacetic acid. The patient was advised to rest and was placed on a restricted diet. He was rendered sugar-free on a diet containing about 140 Gm of available dextrose daily (without the use of insulin). At this time, Dec. 6, 1928, the patient consented to take part in the following experiment.

*Experimental Conditions*—The basal diet of the subject was planned to be similar to the diet given in "Diets of University of Michigan Hospital"<sup>4</sup>. The diet was made up of beef, pork, cream, butter, mayonnaise (diabetic), bacon, eggs, lettuce, celery, squash, peas, corn flakes and Uneeda biscuits. The diet was so arranged as to give approximately equal amounts of dextrose at each of the three meals and yielded daily about 200 Gm of fat, 100 of carbohydrate and 70 of protein (table 1). When it was desired to alter the carbohydrate content this was usually done by varying the number of Uneeda biscuits. The food values of the materials mentioned were determined by analysis by the official methods of the Association of Official Agricultural Chemists<sup>5</sup>. Water, coffee and saccharin were allowed in addition to the foods mentioned. The materials for each meal were weighed with an accuracy of  $\pm 1$  Gm.

Once the diet was adjusted to the proper level it was kept constant within narrow limits. Meals were served at the same time each day.

<sup>3</sup> Joslin. *Treatment of Diabetes Mellitus*, ed. 3, Philadelphia, Lea & Febiger, p. 549.

<sup>4</sup> *Diets of University of Michigan Hospital*, p. 66.

<sup>5</sup> *Official Methods of Analysis*, A. O. A. C., ed. 2.



The artichoke powder was prepared by slicing washed artichokes and drying them in a vacuum drier. The analysis of this powder showed the following composition: moisture, 84, ash, 42, protein, 78, fiber, 3, fat, 12, and total carbohydrate by acid hydrolysis, 75.4 per cent. It should be pointed out that the product fed contained no inulin so that the carbohydrate consisted essentially of soluble sugars, levulose and inuloids.

The urine was collected under toluene. All analyses were made on twenty-four hour samples, the daily sample ending before breakfast at 8 a. m. Nitrogen was determined by the Kjeldahl method and dextrose by the method of Benedict.

Samples of feces were collected and analyzed at once for carbohydrate,<sup>6</sup> nitrogen and fat.<sup>7</sup>

TABLE 1—*Basal Food Intake*

Day	Protein, Gm	Fat, Gm	Carbo- hydrate Gm	Available Dextrose, Gm	Water, Cc	Weight, Pounds	Artichoke Increment Added to Basal Diet in Grams of Carbo- hydrate
1	62	218	52	110	1,510	118	
2	62	218	52	110	1,330	119	
3	65	218	52	112	1,750	119	
4	65	218	66	126	1,150	121	
5	65	218	96	155	1,700	121	
6	65	218	125	180	1,550	119	
7	59	222	155	213	1,350	121	
8	63	236	174	240	1,450	121	
9	74	237	137	201	1,600	118	
10	70	236	105	169	1,250	116	
11	69	236	105	169	1,500	115	
12	69	236	105	169	1,400	116	
13	69	236	105	169	1,200	115	30
14	69	236	105	169	1,500	116	19
15	69	236	105	169	1,150	118	19
16	69	236	105	169	1,000	118	
17	69	236	105	169	1,000	116	
18	69	236	105	169	1,110	117	
19	69	236	105	169	1,700	119	
20	69	236	105	169	1,750	120	
21	64	236	96	156	1,350	119	19
22	69	236	101	165	1,200	118	19
23	69	236	105	169	1,950	117	22
24	69	236	105	169	1,750	119	22
25	69	236	105	169	1,700	118	22
26	69	236	105	169	1,150	117	
27	69	236	105	169	1,350	118	
28	69	236	105	169	1,150	117	
29	69	236	105	169	1,800	118	
30	69	236	105	169	1,200	118	

The data collected on the urine and feces are shown in tables 2 and 3. In no case were appreciable quantities of reducing sugars or hydrolyzable sugars found in the feces. The water intake and daily weight of the subject are also recorded.

## COMMENT

Starting with a basal diet consisting of 62 Gm. of protein, 218 of fat, and 52 of carbohydrate, we increased the intake of available dextrose by the addition of Uneda biscuits until on the fifth day it was found necessary to revise the basal diet upward to avoid feeding a number of

6 Hawk and Bergeim. *Physiological Chemistry*, ed. 9. Philadelphia, P. Blakiston's Son & Company, p. 866.

7 Hawk and Bergeim (footnote 6, p. 329).

Unceda biscuits The revised diet, which was made up of the same materials used before but in increased amounts, contained protein, 69 Gm , fat, 236 Gm , carbohydrate, 105 Gm , and total available dextrose,

TABLE 2—*Urinanalysis*

Day	Volume, Cc	Specific Gravity	Acetone	Nitrogen Gm	Sugar, Gm
1	1,370	1 019	None	10 9	0
2	1,370	1 015	None	8 2	0
3	1,660	1 020	None	14 9	0
4	1,060	1 020	Trace	10 9	0
5	1,470	1 018	Trace	7 8	0
6	1,350	1 015	None	8 4	0 4
7	1,350	1 021	None	9 0	4 8
8	1,200	1 029	None	8 7	29 5
9	1,690	1 022	None	10 2	22 7
10	1,200	1 022	None	8 6	11 2
11	850	1 026	None	9 2	8 7
12	1,000	1 024	None	9 6	7 0
13	980	1 029	None	10 5	17 0
14	1,030	1 025	None	7 9	11 0
15	1,027	1 027	None	9 1	15 4
16	1,100	1 026	None	10 7	18 9
17	660	1 030	None	6 4	13 8
18	1,570	1 019	None	12 7	7 8
19	1,750	1 017	None	10 8	7 5
20	960	1 024	None	10 0	4 6
21	1,470	1 018	None	10 5	3 5
22	1,200	1 018	None	9 1	0
23	1,760	1 015	None	9 6	0
24	1,750	1 017	None	9 2	3 4
25	1,580	1 019	None	9 4	8 5
26	1,210	1 022	None	8 6	6 2
27	1,170	1 022	None	10 3	6 9
28	1,140	1 021	None	9 1	4 5
29	1,270	1 020	None	10 7	5 0
30	1,260	1 020	None	10 2	5 4

TABLE 3—*Data Collected on Feces and Blood*

Day	<i>p<sub>H</sub></i> *	Weight Gm	Nitrogen, Gm	Fat, Gm	Blood	
					Sugar Mg per Hun- dred Cubic Centimeters	Nonpro- tein Nitro- gen, Mg per Hun- dred Cubic Centimeters
1		81	1 1	4 2		
2		81	1 1	4 2		
3		84	1 1	4 2		
4		81	1 1	4 2	97	50
5		119	0 8	5 4		
6		119	0 8	5 4		
7		119	0 8	5 4		
8		119	0 8	5 4		
9	6 88†	119	0 8	5 1		
10	6 15†	119	0 8	5 4		
11	6 00†	221	1 3	1 5	190	55
12		221	1 3	4 5		
13		221	1 3	4 5		
14		56	1 3	3 9		
15		56	1 3	3 9		

\* The *p<sub>H</sub>* of the feces was recorded as follows Sixteenth day, 7 38, eighteenth, 7 4 nineteenth, 7 44, twenty third, 7 28, twenty seventh, 7 48, twenty ninth, 7 4

† Diarrhea

169 Gm On the sixth day, with the addition of 11 Gm of carbohydrate and a total dextrose intake of 180 Gm , the first trace of glycosuria was observed and was close to the tolerance of the patient Had this

diet (180 Gm of available dextrose) been continued, the subject would undoubtedly have excreted several grams of dextrose daily. On the seventh and eighth days, however, the carbohydrate increment was increased, with increased excretion of dextrose, it was decreased again on the ninth and tenth days to 169 Gm of available dextrose. Because of the lag in the excretion of urinary dextrose, sugar continued to be excreted in gradually diminishing amounts to the twelfth day. In calculating the dextrose tolerance (table 4) by averaging the tolerance from the fifth to the twelfth day inclusive, we obtained an average tolerance of 176 Gm. Had this period of feeding the basal diet been extended sev-

TABLE 4—*Period of Basal Diet, Carbohydrate Intake, Outgo and Tolerance in Grams*

Day	5	6	7	8	9	10	11	12
Intake	155	180	213	240	201	169	169	169
Outgo	0	0.5	5	29.5	22.7	14.2	8.7	7
Tolerance	155	179	208	210	178	155	160	162
Average Tolerance								176

TABLE 5—*First Artichoke Period, Carbohydrate Intake, Outgo and Tolerance in Grams*

Day	13	14	15	16	17	18	19	20
Intake	199	188	188	169	169	169	169	169
Output	17	14	15	19	14	8	7	5
Tolerance	182	174	173	150	155	161	162	164
Average Tolerance								165

TABLE 6—*Second Artichoke Period, Carbohydrate Intake, Outgo and Tolerance in Grams*

Day	21	22	23	24	25	26	27	28	29	30
Intake	175	181	192	192	191	169	169	169	169	169
Output	3.5	0	0	3.5	8.5	6	7	5	5	5
Tolerance	172	181	192	188	183	163	162	164	164	164
Average Tolerance										174

eral more days, with a gradually diminishing output of dextrose, the tolerance would have been lowered by 4 or 5 Gm.

*First Artichoke Period*—On the thirteenth day, an addition of dried artichokes (given with water), equivalent to 30 Gm of levulose, was added to the patient's diet, and on the fourteenth and fifteenth days 19 Gm. The subject was then returned to the basal diet until the twenty-first day (table 5). At the first part of this period his tolerance was apparently higher than 176, but gradually decreased. This again is due to the lag in excretion of unused dextrose. The average dextrose tolerance for this period is 165 Gm. From this data, it is obviously impossible to show any increased tolerance to dried artichokes.

*Second Artichoke Period*—A second series of observations were made from the twenty-first to the thirtieth day during which time the

subject was fed 19 Gm of artichoke powder on the twenty-first, 19 Gm on the twenty-second and 22 Gm on the twenty-third, on the twenty-fourth and on the twenty-fifth (table 6). Again the characteristic lag in the excretion of dextrose was seen. That is, at the first of the period even when the patient is fed at a higher level than his tolerance, there is no excretion of dextrose for several days, while after the excretion of dextrose is started, the excretion lasts for several days after the subject ceases to take greater amounts of carbohydrate than he can tolerate. The tolerance during this period was 174 Gm, which checks with the tolerance of the basal diet period (176 Gm). Again these data do not show an increased tolerance due to the artichokes. An average of the two determinations for tolerance during the periods the artichokes were fed was 170 Gm, which is slightly less than the tolerance to the basal diet alone (176 Gm). In any case, there is no evidence that dried artichokes are tolerated better than ordinary starch.

#### SUMMARY

A diabetic subject on a measured diet gave an average tolerance of 176 Gm of dextrose daily. On the addition of powdered dried artichokes and over a period of eighteen days, the average tolerance was 170 Gm. No increased tolerance due to the addition of artichokes is evident, and we conclude that this form of carbohydrate is not tolerated in any greater quantities than starch. The difference in tolerance of 6 Gm between the artichoke period and the basal diet period is within the limits of experimental error for this type of experiment. The average daily tolerance for the entire thirty days of the experiment is 172 Gm. The long lag in the excretion of dextrose is caused by the fact that the available dextrose of the basal diet (169 Gm) is so close to the average calculated tolerance of the patient (172 Gm). The  $p_H$  of the feces was not appreciably changed by the addition of carbohydrate in the form of dried powdered artichokes. We conclude that dried powdered artichokes have no advantage as a diabetic food.

# THE CEREBROSPINAL FLUID IN MYXEDEMA \*

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Observations were made on the cerebrospinal fluid <sup>1</sup> of patients with myxedema before and after the administration of desiccated thyroid. These observations are presented under three headings: (1) the protein content, (2) the distribution of chloride ions between the plasma and the cerebrospinal fluid and (3) the rate of flow.

## THE PROTEIN CONTENT

The measurements,<sup>2</sup> which are summarized in table 1, show two facts: 1. In thirteen of seventeen cases, the protein concentration was high during the period of myxedema.<sup>3</sup> Qualitative tests (the ammonium sulphate ring test of Ross and Jones, and precipitation with an equal quantity of 95 per cent alcohol) indicated that this was true for both albumin and globulin fractions. 2. In all but two cases a well marked drop in the concentration occurred as the basal metabolism approached normal, following the administration of desiccated thyroid. Data on a typical case are plotted in chart 1. In the two cases that showed no decrease, the protein content was normal to begin with.

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~ From the Metabolism and Neurological Laboratories of the Massachusetts General Hospital.

1. The fluid was always removed under "basal conditions."

2. The method of Denis and Ayer (A Method for the Quantitative Determination of Protein in Spinal Fluid, *Arch. Int. Med.* **26**: 436 [Oct.] 1920) was used. This is the best quantitative method known, the error being not greater than 5 per cent.

3. In a few of the cases showing the higher protein concentrations, there was some precipitation in the first six or seven tubes used in the colloidal gold reaction. The precipitation was usually most marked in the "tuberc zone." The reaction usually became normal following the administration of desiccated thyroid.

Qualitative tests usually showed a decrease in the concentration of both protein fractions, to the point where no precipitate could be seen

The change persisted as long as the basal metabolism was held at a normal level by the administration of thyroid, but the concentration of protein tended to return to its previous high level when the administration was stopped (chart 1)

Two observations indicated that the protein content of cerebral fluid was also greater than normal 1 The protein concentration of the fluid obtained after withdrawing large quantities (from 60 to

TABLE 1—*Effect of the Administration of Desiccated Thyroid on the Concentration of Protein and the Basal Metabolic Rate\**

Case	Age	Sex	Laboratory Number	Before Administration of Thyroid						During Administration of Thyroid							
				Basal Metabolic Rate, per Cent Normal	Spinal Fluid				Cells per C Mm	Basal Metabolic Rate, per Cent Normal	Spinal Fluid				Cells per C Mm		
					Concentration of Protein, Mg per 100 Cc	Globulin (Qualitative Test)	Albumin (Qualitative Test)	White			Red	Concentration of Protein, Mg per 100 Cc	Globulin (Qualitative Test)	Albumin (Qualitative Test)		White	Red
1 I G	53	♀	4236	—26	221	+	++	2	0-3	—	3	49	0	0	2	0	
2 I W	50	♀	4224	—21	129	++	++	3	6	++	2	53	+	+	+	0	
3 H L	21	♀	4302	—34	111	+	+	0	1	++19	30	+	+	1	0		
4 M V	17	♀	3934	—17	93	+	+	2	0	++23	32	0	0	+	0		
5 M B	30	♀	4333	—40	90	+	+	1	0	—12	43	+	+	1	0		
6 L C	53	♀	4532	—46	73	+	+	3	0	—10	32	0	0	2	0		
7 I G	48	♀	4671	—43	72	+	+	2	0	—9	36	0	0	1	0		
8 I MeD	43	♀	4123	—24	72	+	+	2	0-70	++	14	0	0	1	0		
9 G M	33	♀	4434	—27	65	+	+	3	0	++7	27	0	0	1	0		
10 A J	33	♀	4681	—23	61	+	+	2	0	—11	34	0	0	2	0		
11 M LeB	43	♀	3532	—24	58	SI +	+	2	0	++15	41	+	+	0	0		
12 M B	57	♀	1836	—21	48	SI +	0	1	0	—5	24	0	0	1	0		
13 A H	18	♀	1807	—22	46	+	+	2	0	++16	27	0	0	2	0		
14 M H	35	♀	4179	—23	38			0	0	++8	44			3	0 to 1		
15 D B	51	♀	4339	—23	34	SI +	?+	2	0	++17	21	0	0	0	8		
16 M M	53	♀	4651	—29	34	0 to SI	+	1	0-222	++6	22	0	0	2	0		
17 J W	47	♀	2680	—22	23	0	0	2	3	++0	31	0	0	0	0		

\* In most of the cases, each figure represents the average of two or more determinations made on different days. The determination of the protein content was usually made on the first 1 cc of fluid removed from the lumbar region. Part of this table was published in the *Journal of Clinical Investigation* 6:251, 1928.

90 cc) from the lumbar region was much greater than is found normally under these conditions 2 In case 1, a cistern puncture was performed, and the protein content of the fluid obtained was high (130 mg per hundred cubic centimeters) These facts suggest that in myxedema fluid of a high protein content may be filtered through the choroid plexus

A high concentration of protein in cerebrospinal fluid is found in so many conditions that in itself it is of little diagnostic significance It is worthy of note, however, that for several months, because of the presence of headaches and ataxia, there was some uncertainty as to whether J G (case 1) had myxedema or a tumor of the brain The latter diagnosis was seemingly corroborated by the finding of a high

pressure as well as a high concentration of protein in the cerebrospinal fluid. The appearance of the patient was not characteristic of the full-blown picture of myxedema. The administration of desiccated thyroid, however, produced a well marked reduction in the concentration of protein, as well as a clinical cure.

Chronic nephritis is, of course, the disease most commonly confused with myxedema. It is of interest that in both diseases one may find albuminuria, a high blood pressure and a high concentration of protein<sup>4</sup> in the cerebrospinal fluid.

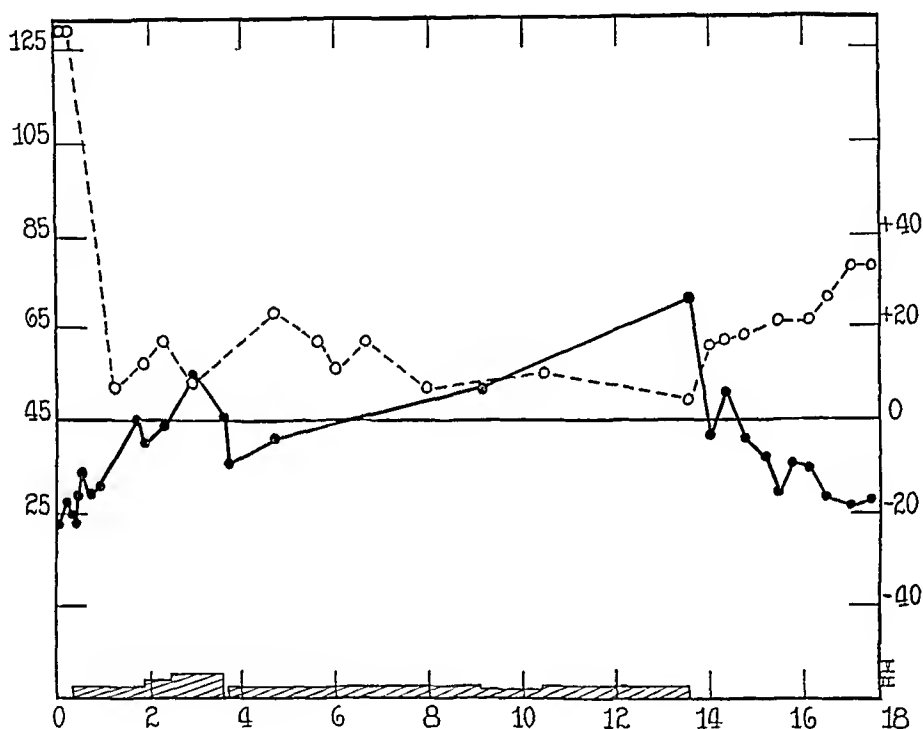


Chart 1—A decrease in the concentration of protein in the cerebrospinal fluid and an increase in the basal metabolic rate following the administration of desiccated thyroid (case 2). The reverse changes occurred when the administration was stopped. The broken line represents the concentration of protein in the cerebrospinal fluid, measured in milligrams per hundred cubic centimeters along the vertical scale at the left. The solid line represents the basal metabolic rate, the percentage being shown by the vertical scale at the right, at the bottom of this scale, the Roman numerals represent grams of desiccated thyroid. The figures along the base of the chart indicate months.

The cause of the high protein content of the cerebrospinal fluid in myxedema is uncertain. A few observations already made<sup>5</sup> indicate

4 Lyttle, J. D., Rosenberg, L., and Hearn, J. E. Cerebrospinal Fluid in Nephritis, *Arch Int Med* **39** 808 (June) 1927.

5 Thompson, W. O., and Alexander, B. The Protein Content of the Cerebrospinal Fluid in Exophthalmic Goiter, *Arch Int Med*, to be published.

that in exophthalmic goiter the concentration is low and increases following a subtotal thyroidectomy. These observations are possibly related in some way to the increase in deposit protein in myxedema<sup>6</sup> and its depletion in exophthalmic goiter.<sup>7</sup> The albuminuria frequently present in myxedema usually disappears or decreases markedly when thyroid is administered. The high concentration of protein in the cerebrospinal fluid and the albuminuria may be, in part, manifestations of the same pathologic condition, namely, an altered permeability of the capillary membranes throughout the body.

TABLE 2—*The Concentration of Chloride in Plasma and Spinal Fluid Before and During the Administration of Desiccated Thyroid (Case 16)*

Date	Basal Metabolic Rate, per Cent Normal	Plasma				Spinal Fluid Chloride as Sodium Chloride, Mg per 100 Cc	Ratio of Spinal Fluid Chloride to Plasma Chloride
		Protein, Gm per 100 Cc	Water,* Gm per 100 Cc	Chloride as Sodium Chloride			
				Mg per 100 Cc	Mg per 100 Cc Plasma Water		
Before Administration of Thyroid							
4/21/27	—30	7.0	93.50	583	624	717	114.9
4/26/27	—28	7.1	93.59	590	630	725	115.1
5/ 9/27	—23	6.8	93.40	601	643	730	113.5
5/13/27	—30	7.2	93.33	595	638	732	114.8
5/17/27	—27	7.5	93.09	588	632	726	111.9
5/23/27	—35	7.6	93.25	586	628	723	115.1
Average							114.7
During Administration of Thyroid							
6/13/27	+ 2	6.4	94.00	629	669	748	111.9
6/21/27	+ 6	6.1	94.25	638	677	758	112.0
6/28/27	+ 5	6.1	94.33	630	668	746	111.7
Average							111.9

\* The concentration of water was determined by drying a known amount of plasma to a constant weight. It was assumed arbitrarily that the specific gravity of plasma was 1.028 before, and 1.026 during the administration of desiccated thyroid.

#### DISTRIBUTION OF CHLORIDE IONS

The ratio of the concentration of the chloride of the cerebrospinal fluid to that of the plasma is often less after the administration of desiccated thyroid. Data on a typical case are recorded in table 2. This decrease in the ratio is associated with an increase in the total volume of plasma and in the concentration of plasma water, and with a diminution in the concentration of protein in plasma. The obser-

6 Magnus-Levy, A. Metabolism in Diseases of the Ductless Glands, in Noorden, C. von. Metabolism and Practical Medicine, Chicago, W. T. Keener and Company, 1907, vol. 3, p. 983. Boothby, W. M., Sandiford, I., Sandiford, K., and Slosse, J. The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects, *Tr. A. Am. Phys.* 40: 195, 1925.

7 Magnus-Levy (footnote 6, first reference).



vation is in harmony with numerous observations made by Fremont-Smith and Dailey,<sup>8</sup> which suggest that there is a relation between variations in the ratio of the chloride content of the spinal fluid to that of the plasma and variations in the concentration of protein in plasma

#### RATE OF FLOW

With the patient in the horizontal lateral position, a lumbar puncture was performed in the usual manner. All readily available fluid was slowly drained off until the pressure was zero, and the rate of flow about uniform. All fluid that flowed from the needle was then collected for an hour. This was done frequently on three patients, both

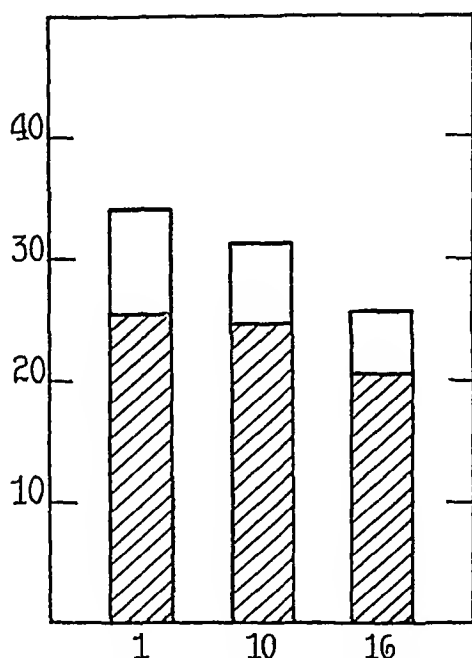


Chart 2—The average rate of flow of the cerebrospinal fluid before (cross hatched areas) and after (total height of columns) the administration of desiccated thyroid. The vertical scale at the left shows the number of cubic centimeters of spinal fluid obtained. The case number appears below its respective column.

before and after the administration of desiccated thyroid. The average figures for each case under both conditions are plotted in chart 2. Owing to the crudeness of the method, we do not feel justified in concluding that the recorded increase in flow after the administration of thyroid is the result of an increased rate of formation. We feel, however, that the experiments indicate that the administration of thyroid

<sup>8</sup> Fremont-Smith, F, and Dailey, M. E. Unpublished data, referred to by Fremont-Smith, F. The Nature of the Cerebrospinal Fluid, *Arch Neurol & Psychiat* **17** 317 (March) 1927.

does not decrease the rate of formation of cerebrospinal fluid, as Frazier and Peet<sup>9</sup> claimed

#### SUMMARY AND CONCLUSIONS

1 The concentration of protein in cerebrospinal fluid (lumbar) is high in most cases of myxedema and usually drops to within normal limits following the administration of desiccated thyroid

2 The concentration of protein in cerebral fluid also appears to be high, although less than that in lumbar fluid

3 Owing to the high concentration of protein in the cerebrospinal fluid, myxedema may, in rare instances, be confused with tumor of the brain

4 The ratio of the chloride content of the spinal fluid to that of plasma is often less after the administration of desiccated thyroid

5 The rate of flow of cerebrospinal fluid is not less, and may be greater after the administration of thyroid

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9 Frazier, C. H., and Peet, M. M. The Action of Glandular Extracts on the Secretion of Cerebro-Spinal Fluid, *Am J Physiol* **36** 464, 1914-1915

# THE DIURETIC ACTION OF THE PARATHYROID EXTRACT †

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The literature of recent years contains several reports concerning the diuretic effect of parathyroid hormone (Mason,<sup>1</sup> Meakins,<sup>2</sup> Hueper,<sup>3</sup> McCann<sup>4</sup>) As the mechanism of this action is not known, the report of some observations made on the kidneys of dogs given injections with parathyroid extract-Collip may be of interest

Sympathicotonic spastic contractions of the vasa afferentia of the glomeruli are considered by Volhard<sup>5</sup> and Jungmann<sup>6</sup> as the cause of oliguria and anuria in glomerulonephritis and reflex anuria This conception has found practical expression in several methods used in the therapeutic management of these conditions as the anesthesia of the splanchnic nerves after Kappis (Neuwirt<sup>6</sup>), general anesthesia to lessen the splanchnic tonus, parenteral injection of blood and protein substances to bring about a change in the tonus of the vegetative nervous system, denervation of the pedicle of the kidney to cause an interruption of the renal nervous supply, especially that by the splanchnic nerve, decapsulation of the kidney to relieve the capsular pressure and to produce simultaneously a partial denervation of the kidney, a procedure warmly recommended by Volhard

During the course of experiments with dogs receiving injections of parathyroid extract, I made the observation that this hormone has a strong vagotonic effect, evidenced by a decrease of the pulse rate, prolongation of the systole, shortening of the diastole, hyperemia of the vessels of the abdominal organs, and intensification of the peristalsis of

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† Submitted for publication, May 24, 1929

‡ From the Department of Pathology, Loyola University School of Medicine and Laboratories of Mercy Hospital

1 Mason, E H A Case of Chronic Nephritis Treated with Collip's Parathyroid Extract, Canada M A J **16** 538, 1926

2 Meakins, J C Reaction of Chronic Nephrosis to Thyroid and Parathyroid Medication, J A M A **89** 149 (July 9) 1927

3 Hueper, W Metastatic Calcifications in the Organs of the Dog After Injections of Parathyroid Extract, Arch Path **3** 14 (Jan) 1927

4 McCann, W S Diuretic Action of Parathyroid Extract-Collip in Certain Edematous Patients, J A M A **90** 249 (Jan 28) 1928

5 Volhard, F Ueber die Behandlung der Nierkrankheiten, Ztschr f Urol **19** 5, 1925

6 Jungmann, P Die Pathogenese der Anurie und die Grundlagen ihrer Behandlung, Klin Wchnschr **6** 241, 1927

the stomach and intestine. When the amount of the injected parathyroid extract was adjusted in such a way that the blood calcium level was raised to about 15 mg. in 100 cubic centimeters of blood, a markedly increased excretion of urine was noticed. Dogs killed during this stage, on histologic examination of the kidneys showed that the blood vessels, especially the glomerular capillaries, were extremely distended with blood. There were no other changes observed in the kidney, especially no tubular degenerations or calcium precipitations.

#### COMMENT

The conclusion may therefore be justified that the increased excretion of urine observed in these dogs was at least to some extent due to the active hyperemia of the renal vessels caused by the increased vagotonus resulting from the injections of the parathyroid extract. As injections of parathyroid extract are not dangerous to the patient if the blood calcium level is properly controlled, this method may be tried for relief from oliguria and anuria before more radical and dangerous measures are used. It may be noted furthermore that the increase of the calcium level in the blood which is frequently found to be lowered in glomerulonephritis will have a beneficial effect on the often concomitant hypertension and will help to regulate favorably the heart action. Medication with parathyroid extract may represent a causative treatment in reflex anuria, but is of only symptomatic value in the therapeutic management of glomerulonephritis.

# OPIUM ADDICTION

## VIII THE EFFECTS OF INTRAMUSCULAR AND INTRAVENOUS ADMINISTRATION OF LARGE DOSES OF MORPHINE TO HUMAN ADDICTS <sup>†</sup>

ARTHUR B LIGHT, M D

AND

EDWARD G TORRANCE, M D

PHILADELPHIA

Wide variations in the quantity of the drug used and also in the frequency of administration to prevent withdrawal symptoms are encountered among different human addicts as well as in the same addict at various periods during addiction. This variation is found not only in dosage and frequency of administration, but also in the methods of administration. The choice as to the latter in 95 per cent of our cases was the hypodermic method, but sniffing of heroin, oral administration, pipe smoking of opium and intravenous administration were also encountered. With these variations in mind we administered additional amounts, both intramuscularly and intravenously, in order to determine, first, what physiologic effects are brought about in human addicts by quantities greater than those required to prevent withdrawal symptoms, second, whether abrupt withdrawal for a period of forty-eight hours decreases the intravenous tolerance of the addict, and third whether these additional amounts prolong the period of comfort on the part of the addict.

Samples of blood were analyzed for morphine by Dr. A. K. Balls <sup>1</sup> of the Department of Pharmacology, University of Pennsylvania, immediately following the completion of the injection.

### EXPERIMENTAL PROCEDURE

Five addicts, one of whom was at times accustomed to the intravenous administration of the drug, while the other four used the hypo-

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<sup>†</sup> Submitted for publication, March 5, 1929.

\* From the Narcotic Wards of the Philadelphia General Hospital.

\* Expenses of this committee were defrayed by the Committee on Drug Addictions, New York City, and were carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction in the Narcotic Wards of the Philadelphia General Hospital which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia.

1 Balls, A. K., and Wolff, W. A. The Determination of Morphine, *J. Biol. Chem.* **80** 379 (Dec.) 1928.

dermic method, volunteered as subjects for the experiments planned. All of the experiments, whether the drug was given intramuscularly or intravenously, were made while the patients were reclining in bed for at least half an hour without having had breakfast. Except in the cases in which morphine was withheld for a period of forty-eight hours, the regular dosage was given intramuscularly, usually about 8-30 a.m.

The morphine sulphate solution used in these experiments was especially prepared by the department of pharmacology of the University of Pennsylvania in an isotonic solution of sodium chloride, 5 cc containing 2 grains (0.13 Gm.) of morphine sulphate. When the drug was given intramuscularly, the point of injection was usually over the anterior part of the chest or in such areas as appeared to be free from recent injections. The intravenous administration was always given into the median basilic vein. In all cases of intravenous administration, 2 grains was given at each injection, except in one case following a period of withdrawal for forty-eight hours, when at the close of the experiment the dosage for several injections was raised to 4 grains (0.26 Gm.).

The observer who administered the drug reported the general behavior and color of the skin of the subject, as well as any remarks on his part. Another observer confined his attention to the blood pressure, a third to the counting of the pulse and a fourth to the respirations. The figures for blood pressure are the average for as many as could be accurately taken in a five minute period. The figures for pulse rate and respirations are the averages of a five minute count. In the protocols of two experiments given in this paper are found the actual figures and the remarks made by the addict during the entire period of administration. Samples of blood for the analyses reported were taken just before the administration of the drug was begun and, as a rule, about fifteen or twenty minutes following the last dosage. In four cases, electrocardiographic studies were made preceding the administration and immediately following the last dosage given.

The actual time required for each injection of 2 grains varied from one minute and twenty seconds to four minutes and twenty-two seconds, depending on the reaction of the patient.

## RESULTS

Tables 1, 2 and 3 contain the data obtained from the various experiments. Chart 1 shows graphically the changes in blood pressure, respiration and pulse rate obtained in an experiment in which 30 grains (1.95 Gm.) of morphine sulphate was given intravenously to an addict over a period of two hours and twenty-four minutes, he having previously received his normal dosage of 17 grains (1.1 Gm.) in twenty-four hours. Protocols 1 and 2 give the actual determinations of blood pressure, pulse and respiratory rates during the intravenous administration.

TABLE 1—*The Effects of the Administration of Additional Amounts of Morphine Sulphate Intramuscularly to Human Opium Addicts*

Time and Case No	Dosage of Drug, Grains	Blood Pressure	Respirations per Minute	Pulse per Minute	P-R Interval, Seconds	pH of Blood	Sugar, Mg per 100 Cc	Urea Nitrogen, Mg per 100 Cc	Dry Matter of Whole Blood
Case 26-33									
9 55 a m		104/61	10	55	0 155	7 33	90	11	20 40
9 57 a m	5	104/61							
11 11 a m	6								
11 53 a m	6								
Total	17								
12 00 noon		101/55	9	60	0 160	7 32	92	10	19 16
Case 26-85									
9 50 a m		90/68	8	66	0 156	7 40	80	12	20 23
9 56 a m	3								
10 56 a m		98/60	8	60					
11 11 a m	4								
11 52 a m	4								
Total	11								
12 29 p m		102/64	10	58	0 172	7 38	90	9	19 69
Case 26-39									
10 34 a m		116/68	14	60					
10 35 a m	5								
11 07 a m		108/62	13	59					
11 10 a m	5								
Total	10								
11 31 a m		106/64	14	60					

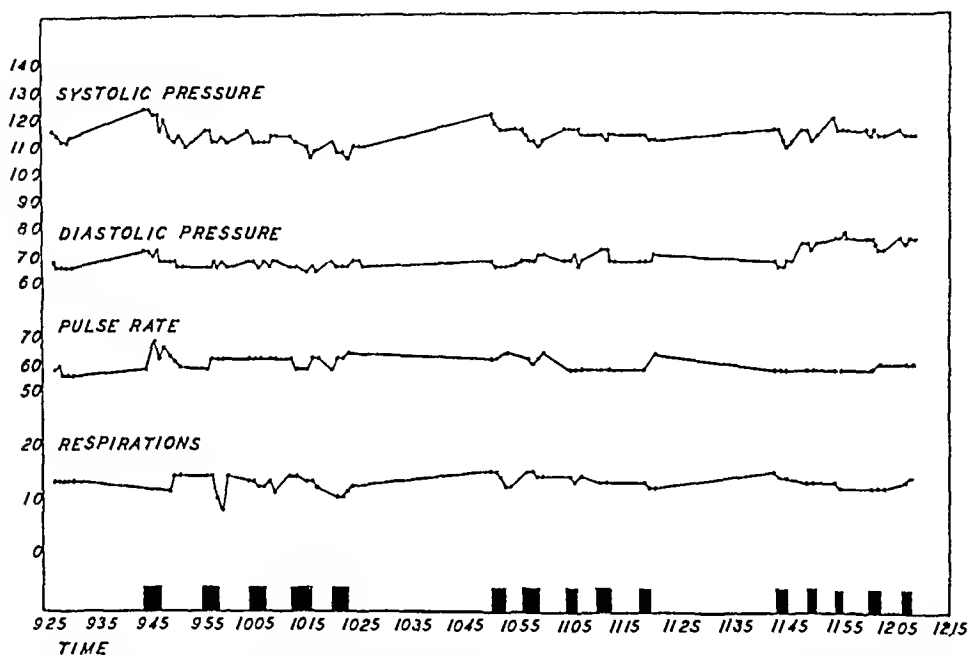
TABLE 2—*The Effects of the Administration of Additional Amounts of Morphine Sulphate Intravenously to Human Opium Addicts*

Case No	Pulse	Respirations	Blood Pressure	P R Interval, Seconds	Hemo globin	Dry Matter of Whole Blood	Percentage Oxygen Content of Venous Blood	Saturation of Venous Blood	pH of Blood
26-21									
Before injection	85	22	126/68	0 176	14 9	20 83	9 3	62 4	7 45
After injection	68	18	118/76	0 184	14 4	20 27	11 3	78 5	7 41
14 grains, 2 hours*									
26-39									
Before injection	60	14	115/68	0 160					
After injection	62	14	116/68	0 160					
30 grains, 2 hours 23 minutes*									
26-56									
Before injection	72	12	117/69		Erythrocytes 4,560,000	Leukocytes 6,600			
After injection	73	11	122/70		4,640,000	5,800			
6 grains, 1 hour 37 minutes									

\* Analysis of the blood for the presence of morphine sulphate by Dr Balls (J Biol Chem 80 379 [Dec] 1928) of the Department of Pharmacology, University of Pennsylvania, resulted in the finding of less than 1 mg per 25 cc of blood, equivalent to approximately 4 grains in total blood

of morphine sulphate to the same addict during his regular dosage and following a forty-eight hour period of withdrawal. The protocols also contain the remarks of the patient as well as such observations as were deemed important.

In the three cases in which the morphine was administered intramuscularly in dosages of six, four and three times the amount to which the addicts were accustomed, no significant changes in the pulse, respiration, blood pressure, P-R interval, blood reaction or blood content in dry matter, urea nitrogen or sugar could be found. In one case the blood pressure fell from 116 systolic, 68 diastolic to 106 systolic, 64 diastolic, but in another it rose from 90 systolic, 68 diastolic to 102 systolic, 64 diastolic, in the third, the change was within the error of reading.



Effect on pulse rate, blood pressure and respiration of 30 grains (1.95 Gm.) of morphine sulphate given intravenously to a human addict over a period of two hours and twenty-four minutes. The shaded areas indicate the time of injections, of 2 grains each.

When the drug was administered intravenously to three different patients in dosages of seven, nine and six times the usual quantity, there was no change in the pulse rate, respiration and blood pressure in two. Hemoglobin, the dry matter of the whole blood and the blood reaction showed no significant change in the one case in which analysis of the blood was made. In one addict given nine times the usual dose, the P-R interval remained the same but in the subject given seven times the usual dosage it was prolonged from 0.176 to 0.184 second. In the latter case however the pulse rate dropped from 85 to 68 per minute, the blood pressure fell from 126 systolic, 68 diastolic to 118 systolic,



76 diastolic, and the respirations from 22 to 18 per minute. This patient (case 26-21) showed definite signs of fear before the injections were begun. As the injections proceeded and no untoward results were felt, whether because of the action of the drug or not, this addict showed less apprehension, which we believe to be the factor in these changes. The percentage of oxygen saturation of the venous blood taken from the same vein at the elbow rose from 62.4 to 78.5. A count of the red and white blood cells made in one case showed no change.

TABLE 3—*The Effects of the Administration of Morphine Sulphate Intravenously Following a Forty-Eight Hour Withdrawal Period in Human Opium Addicts*

	Case 26-21		Case 26-39	
	At the End of 48 Hours Withdrawal Before Administration of the Morphine Sulphate	Following Administration of the Morphine Sulphate, 11 Grains, in 1 Hour 16 Minutes	At the End of 48 Hours Withdrawal Before Administration of the Morphine Sulphate	Following Administration of the Morphine Sulphate, 20 Grains, in 53 Minutes*
Pulse	80	96	72	79
Respirations	21	18	11	11
Blood pressure	132/74	122/70	109/64	102/63
Erythrocytes	5,150,000	5,550,000	5,240,000	5,420,000
Leukocytes	10,800	12,200	13,300	12,700
Differential count				
Polymorphonuclears	77	79	76	73
Lymphocytes	20	19	21	25
Transitionals	2	1	3	2
Basophils	1	0		
Large mononuclears	0	1		
Baskets	4	5		
Arneth				
Old	68	61	68	67
New	32	39	32	33
Fragility				
Complete	36	36	32	30
Partial	44	44	48	48
Coagulation	2 min	1 min 50 sec	2 min	1 min 40 sec
pH	7.44	7.39		
Carbon dioxide capacity	54	56		
Hemoglobin	16.1	16.9		
Percentage of saturation of oxygen of venous blood	61.7	84.1		
Dry matter of whole blood	22.22	22.59		
Dry matter of plasma	9.59	9.64		

\* Analysis of the blood for the presence of morphine sulphate by Dr. Balls of the Department of Pharmacology, University of Pennsylvania, resulted in the finding of less than 1 mg. per 25 cc. of blood.

The two cases studied during the intravenous injection of morphine sulphate following a withdrawal period of forty-eight hours both showed rises in the pulse rate and a slight fall in the pressure. Respirations decreased slightly in one and remained the same in the other. There was a rise in the number of red blood cells of 400,000 per cubic millimeter in the one case and of 180,000 in the other. The white blood cell count per cubic millimeter of blood fell slightly in one and rose correspondingly in the other.

The differential counts, Arneth counts and the fragility of the cells as well as the coagulation time remained practically the same. In one case, the dry matter of the whole blood rose slightly as did the hemo-

globin, but the dry matter of the plasma remained the same. The blood  $p_{\text{H}}$  fell from 7.44 to 7.39, the carbon dioxide capacity remained the same. There was a rise of from 61.7 to 84.1 in the percentage of oxygen saturation of venous blood drawn from the vein.

The behavior of the addicts following the large doses given both intravenously and intramuscularly is of considerable interest. In the three cases studied following intramuscular injection, it was impossible to detect any change in appearance. One addict stated that he felt "loaded", the other two expressed their feelings as being unchanged during the injections. There was no evidence of drowsiness. Interest was shown in the surroundings, and an occasional cigaret was smoked. One subject read the newspaper when observations were not being taken. All three requested their usual dosage at the next regular interval and ate their regular meals.

Two of the three addicts who acted as the subjects for intravenous injections of morphine during regular administration served also as the subjects for the intravenous administration following a forty-eight hour withdrawal period. The patient in case 26-39 had occasionally used the intravenous method of administration during addiction outside the ward but while in the ward was given the drug hypodermically.

During the intravenous administration of the drug during the period of regular dosages, the patients in cases 26-21 and 26-56 complained at times of itching and severe tingling in the extremities, back of the neck and face, as well as over the anterior part of the chest, which would last for a minute or two while the drug actually was being injected. At one time during the injection, the addict in case 26-21 complained bitterly of a pain in his head as if he "were hit in the head with a baseball bat" and again, as he expressed it, "as if someone were jabbing his knuckles in the back of my head." Yet a few minutes later he would state that he felt fine and was as well as if he had never taken drugs in his life. At the time that the patients stated that they experienced these sensations, no changes could be noticed by the observers in the pulse rate, respiration and blood pressure, although there appeared to be an increased redness of the face, neck and anterior part of the chest. On the other hand, the addict in case 26-39 who received by far the largest doses during the intravenous administration scarcely felt any of the sensations described by the other two. It is true that he had at times been accustomed to intravenous administration and he said that he was familiar with these sensations but that he felt them only slightly and not enough to annoy him.

Protocol 2 gives in detail the observations and remarks of patient 26-39 during the intravenous administration following the forty-eight hour withdrawal period. They need no comment, except again to call attention to the fact that during the last dose of 4 grains the subject

requested a hypodermic injection into the muscle. The experiment was finished at 11 05 a m, at which time he was given 3 grains hypodermically. At 3 p m, he requested another hypodermic injection of 3 grains. Between these two intervals, he was about the ward as usual, read a newspaper and ate a hearty lunch.

The reaction of patient 26-21 who received 11 grains intravenously in one hour and sixteen minutes following a forty-eight hour withdrawal period was similar to that in patient 26-39. He was considerably more nervous than patient 26-39. The violent twitching of the labial muscles present before the injections were begun became considerably less evident only after the seventh grain was injected, at an interval of one hour and six minutes after the injection of the first two grains. These twitchings were still slightly present after the last dosage of a total of 11 grains. This patient complained at times of feeling on fire and of "that awful tingling in the body." However, careful observations of blood pressure and pulse and respiration rates again showed no marked changes during these complaints. His face and neck and the anterior part of the upper half of the chest also showed the brilliant red color found in case 26-39, and he scratched this area at frequent intervals. At the end of the experiment he complained of feeling drowsy, but he immediately got up from the bed, started conversing with several other addicts and ate his regular lunch. He slept for a short interval following his lunch, but at 4 p m requested his usual dosage of 2 grains of morphine hypodermically.

#### PROTOCOLS

PROTOCOL 1 (case 26-39) — *The Intravenous Administration of 30 Grains (19 Gm) of Morphine Sulphate in Two Hours and Twenty-Four Minutes*

This subject, aged 29, had been addicted to the use of the drug for 13 years (?). He was 5 feet 10½ inches (179 cm) tall and weighed 220 pounds (99.7 Kg). He had received a dosage of morphine sulphate of from 21 to 25 grains (1.36 to 1.62 Gm) per twenty-four hours in the ward for the last five days. On the day of the experiment, Feb 14, 1927, the patient did not receive breakfast.

8 30 a m      Morphine sulphate, 4 grains (0.26 Gm) given hypodermically  
8 45 a m      Patient reclining in bed

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
9 26 a m				
9 27 15 seconds	118/70	14	60	
9 27 55 seconds	116/68	14	61	No comment on part of patient
9 28 37 seconds	114/68	14	58	
9 29 25 seconds	114/68	14	58	
9 30 10 seconds	116/68	14	58	
9 44 a m	Intravenous injection of 2 grains (0.13 Gm) morphine sulphate begun			
9 44 22 seconds	126/74		60	

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
9 45 08 seconds	126/74			
9 45 10 seconds				Felt a little tingling sensation "I have not got the kick yet"
9 45 46 seconds	124/72		70	
9 46 25 seconds	124/74			
9 46 36 seconds				Did not feel anything
9 47 01 seconds	118/70		64	
9 47 49 seconds	122/70		68	
	Injection finished			
9 49 07 seconds	116/70	12	65	
9 50 12 seconds	114/70	15	63	
9 51 07 seconds	116/68	15	61	
9 51 49 seconds	112/68			Patient did not feel the slightest thing "No kick at all"
9 55 a m	Second dosage of 2 grains of morphine sulphate, intravenously, begun			
9 56 09 seconds	118/68	15	60	
9 56 46 seconds	118/68			
9 57 29 seconds	114/70	15	64	
9 58 24 seconds	114/68	11	64	
	Injection finished			
9 59 26 seconds	116/70	9	64	Patient dozed "How do you feel?" "Just flushing up a little, that's all"
10 00 37 seconds	114/68	15		
10 04 a m	Third dosage of 2 grains of morphine sulphate, intravenously, begun			
10 04 49 seconds	118/70	14	64	
10 05 34 seconds	114/70	14	64	
10 06 25 seconds	114/68	13	64	
10 07 16 seconds	114/70	13		
	Injection finished			
10 08 11 seconds	114/68	14	64	Patient denied any feeling of tingling or flushing up "I do not feel any different, just the same"
10 08 54 seconds	116/70			
10 09 47 seconds	116/70	12	64	
10 12 a m	Fourth dosage of 2 grains of morphine sulphate, intravenously, begun			
10 12 56 seconds	116/68	15	64	
10 13 58 seconds	114/68	15	60	
10 15 02 seconds	112/66	14	60	
10 15 54 seconds	108/68	14	64	
	Injection finished			
				Patient still said, "I feel all right"

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
10 16 55 seconds	110/66	13	64	
10 20 a m	Fifth dosage of 2 grains of morphine sulphate, intravenously, begun			
before start	114/70	11	60	
10 21 26 seconds	110/68	11	64	
10 22 15 seconds	110/68	12	64	
10 23 24 seconds	108/68	13	66	
	Injection finished			
10 24 06 seconds	112/70			
10 25 00 seconds	112/70			Patient felt drowsy, dozed just sitting up in chair smoking Said he was not hungry
10 25 48 seconds	112/68			
10 30 a m	Blood drawn			
10 50 a m	Sixth dosage of 2 grains of morphine sulphate, intravenously, begun			
10 50 39 seconds	124/70	16	64	
10 51 30 seconds	120/68	16	64	
10 52 15 seconds	118/68	15		
10 53 01 seconds	118/68			
	Injection finished			Patient still denied any sensations "I feel all right"
10 53 42 seconds	118/68	13	66	
10 54 30 seconds	118/68	13		
10 56 a m	Seventh dosage of 2 grains of morphine sulphate, intravenously, begun			
10 56 04 seconds	118/70			
10 56 44 seconds	116/68			
10 57 31 seconds	114/70	16	64	
10 58 16 seconds	114/70	16	62	
10 59 02 seconds	112/72	15	64	"I feel all right No, I have not felt any tingling"
	Injection finished			
10 59 53 seconds	114/72	15	66	
11 04 a m	Eighth dosage of 2 grains of morphine sulphate, intravenously, begun			
before start	118/70			
11 04 40 seconds	118/70			
11 05 40 seconds	118/72	15	60	
11 06 23 seconds	118/68	14	60	
11 07 03 seconds	Injections finished			
11 07 08 seconds	116/70	15	60	"I feel all right"
11 10 a m	Ninth dosage of 2 grains of morphine sulphate, intravenously, begun			
11 10 41 seconds	116/74			
11 11 16 seconds	112/74	14	60	

	Time	Blood Pressure	Respiration	Pulse Rate	Remarks
11	12 01 seconds	116/70			"That's the time I felt it" Itching around face and at back of neck
11	12 58 seconds	116/70	14	60	
11	13 59 seconds	Injection finished Patient lay on the bed most of the time with his eyes closed Looked peaceful enough Was not much interested in the actions going on around him "What am I thinking about?" "Oh, nothing, just resting Just thinking of things in gen- eral, nothing in particular I am perfectly satisfied I am thinking of what I am going to eat" "Oh, no, I do not think I could stay this way the rest of my life"			
11	18 a m	Tenth dosage of 2 grains of morphine sulphate, intravenously, begun			
11	18 52 seconds	116/70			
11	19 35 seconds	116/70	14	60	
11	20 15 seconds	114/70	13		
11	20 54 seconds	Injection finished			
11	21 04 seconds	114/72	13	66	
11	22 a m	Blood drawn			
11	43 a m	Eleventh dosage of 2 grains of morphine sulphate, intravenously, begun			
11	43 22 seconds	118/70			
11	43 56 seconds	118/68	16	60	
11	44 40 seconds	114/68	15	60	
11	45 25 seconds	112/70	15	60	Patient said he felt the "pins and needles" slight- ly that time
11	46 04 seconds	Injection finished			
11	46 10 seconds	114/70			
11	48 a m	Twelfth dosage of 2 grains of morphine sulphate, intravenously, begun			
11	48 12 seconds	118/76	14	60	
11	49 01 seconds	118/76	14	60	
11	49 57 seconds	114/74			
		Injection finished			
11	50 30 seconds	116/76			
11	54 a m	Thirteenth dosage of 2 grains of morphine sulphate, intravenously, begun			
	before start	122/78			
11	54 52 seconds	118/78	14	60	
11	55 42 seconds	118/80	13	60	
11	56 00 second	Injection finished "Outside of that little tingling sensation, I don't feel anything"			
11	56 20 seconds	118/78			
12	00 noon	Fourteenth dosage of 2 grains of morphine sulphate, intravenously, begun			
	before start	118/78			
12	00 46 seconds	116/78			
12	01 35 seconds	118/76	13	60	

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
12 02 22 seconds	116/74	13	62	
12 02 48 seconds	Injection finished			
12 03 04 seconds	116/74	13		
12 06 p m	Fifteenth dosage of 2 grains of morphine sulphate, intravenously, begun			
12 06 42 seconds	118/78			
12 07 20 seconds	116/76	14	62	
12 07 52 seconds	116/78			
12 08 24 seconds	Injection finished			
12 08 29 seconds	116/78	15	62	
12 45 p m	Blood drawn			
12 47 p m	Electrocardiogram			
	Twice during the experiment, the patient asked for and received a glass of water			

PROTOCOL 2 (case 26-39) — *The Intravenous Administration of 20 Grains (1.3 Gm.) of Morphine Sulphate in a Period of Fifty-Six Minutes Following a Withdrawal Period of Forty-Eight Hours*

This subject, aged 29, had been addicted to the use of the drug for years (?). He was 5 feet 10½ inches tall and weighed 216 pounds (98 Kg). The daily dosage in the ward for the last twenty-three days has been from 21 to 25 grains of morphine sulphate per twenty-four hours, eighteen days previous to this experiment he received 30 grains of morphine sulphate intravenously in a period of two hours and fifty-three minutes. For the past forty-eight hours, the drug had been withheld.

At 9 27 a m, the patient was reclining in bed. The visible signs of withdrawal were frequent yawning, lacrimation, dilated pupils, slight cough, difficulty in breathing through the nose, occasional tremor of the right leg and extreme nervousness manifesting itself mostly in begging for the experiment to begin. The subject appeared to be suffering with a severe cold. No rise in temperature occurred.

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
9 32 25 seconds	110/64	11	75	Yawned
9 33 01 seconds	110/66	12	74	
9 33 36 seconds	108/62	12	74	Yawned
9 34 08 seconds	110/64	12	70	
9 34 47 seconds	110/64			
9 36 a m			72	Coughed
9 38 a m				
9 38 40 seconds	110/64			
9 39 18 seconds	110/66	16	71	
9 40 05 seconds	110/64			Coughed
9 40 35 seconds	110/64	16	75	
9 41 10 seconds	112/64			Yawned
9 41 18 seconds		14	76	Coughed
9 41 54 seconds	114/66			
9 42 35 seconds	112/64	16	73	
9 42 40 seconds				Coughed
9 43 23 seconds	112/68	14	72	Yawned, moving feet

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
9 44 05 seconds	112/68			Yawned, moving feet
9 44 a m	Coughed and yawned			
9 45 a m	Testing of reflexes of knees			
9 49 a m	Blood drawn			
9 52 a m	Yawned			
9 58 a m	Patient rose up in bed in anticipation			
10 00 a m	Yawned and said "Give me the shot and a damp towel for the back of my neck, that's all" Yawned twice more			
10 02 a m	How do you feel?" "I am aching all over and yawning I feel sick at my stomach There's nothing quiet about me My nose feels stopped up I could vomit Gaggling, that's what that cough is, but the minute you shoot it in the vein I will feel better"			
10 05 a m	First dosage of 2 grains of morphine sulphate, intravenously, begun			
10 05 12 seconds	116/68			
10 06 05 seconds	114/66	24	70	
10 06 12 seconds				"I feel it now—my nose is cleared up No other sensation My nose has stopped running It dries right up"
10 07 01 seconds	116/64	12	72	No other sensations No tingling or pain in back of neck "You are going too slow"
10 07 13 seconds	Injection finished			
10 07 45 seconds	110/66	12		
		11		
10 11 a m	Second dosage of 2 grains of morphine sulphate, intravenously, begun			
before start	112/68			
10 11 15 seconds	114/66			
10 11 57 seconds	116/68			
10 12 12 seconds		12	72	"I can feel it now Through the shoulders Sort of pulls together Your nerves get quiet I feel warmer now"
10 12 28 seconds				"My cold has gone now Eyes are not watering, but you do not get relieved, not yet Twitches have not gone yet Only in that right leg"
10 12 56 seconds	112/70	11	72	
	Injection finished			
10 13 35 seconds	112/76	11	72	
10 16 a m	Third dosage of 4 grains of morphine sulphate, intravenously, begun			
10 16 25 seconds	108/68			



Time	Blood Pressure	Respiration	Pulse Rate	Remarks
10 16 55 seconds	112/70	20	80	"My knees are beginning to relax"
10 17 23 seconds		12 ( $\frac{1}{2}$ min)		
10 17 30 seconds	112/68		80	
10 18 20 seconds	112/68			"Twitching of legs and knees I have that twitchy feeling in just that right leg"
10 19 14 seconds				"Now I am just getting that 'weight' in my stomach"
10 19 20 seconds	108/70			"I am beginning to flush up You don't get that pins and needles when you go so slow"
10 19 26 seconds			80	
10 20 26 seconds	110/68			
10 20 55 seconds				"Now I got that tinge that sort of makes your face and hands swell up"
	Injection finished			
10 21 20 seconds	108/68			Patient's ears were extremely red but he said that they did not burn
10 24 a m	Fourth dosage of 4 grains of morphine sulphate, intravenously, begun			
10 24 30 seconds	112/68			
10 25 25 seconds		13	62	Patient denied feeling drowsy "I feel better than I did, yes"
10 25 30 seconds				
10 25 34 seconds	108/68			"Could I stand more? Sure, your nerves seem to eat it right up as soon as you get it"
10 26 15 seconds	110/68	12	84	
10 27 25 seconds		11	86	"I feel a little tingling in the back of my neck"
10 27 35 seconds	108/66			
	Injection finished			
10 28 30 seconds	106/68	11	86	
	Patient complained of severe itching and sat up in bed scratching himself violently on the face, which was flushed He complained of that tingling sensation over this area			
	A brilliant red flush was now noted over the face, neck and upper part of the chest anteriorly This did not extend to the arms or the lower part of the chest and was not noted elsewhere Patient complained of a terrific itching over the red area, this was especially marked at the back of the neck He rubbed and scratched furiously for about five minutes and for the rest of the experiment the itching was present, but in a lesser degree			

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
10 43 a m	Reflexes of both knees and ankles were tested by Dr Stanley Cobb of Boston, who expressed the opinion that they seemed active enough and appeared practically normal			
10 48 a m	Fifth dosage of 4 grains of morphine sulphate, intravenously, begun			
10 49 01 seconds	104/64		76	
10 49 43 seconds	102/64			
10 49 50 seconds				Patient lay with closed eyes and when asked about his thoughts said "I was just thinking about McCarthy, a n o t h e r patient here, that's all"
10 50 21 seconds	102/62		78	
10 50 45 seconds				"How do you feel?" "All right My nerves are all right Yes, I could stand another shot"
10 50 55 seconds	102/64			
10 51 55 seconds	102/62		80	
	Injection finished			
10 52 55 seconds	102/64		78	
	Patient scratched the palm of his right hand He said he was hungry "No, the weight in my stomach has gone That lasted only a very few minutes It was a depressed feeling down there, something heavy down there"			
10 58 a m	Sixth dosage of 4 grains of morphine sulphate, intravenously, begun			
10 58 20 seconds	104/64			
10 59 02 seconds	102/64		76	
10 59 25 seconds				"I feel all right now and have for the last ten minutes I would like a hypo in the muscle I will wait for fifteen minutes though"
10 59 42 seconds	102/64			
11 00 15 seconds	104/66		80	
11 00 40 seconds				Felt kind of dry in the mouth (He asked for a glass of water) "My nose is all free and everything now I am not coughing and my stomach is all right Yes, I am comfortable now"
11 01 05 seconds	102/64			"No, I am not drowsy" (although patient spoke slowly) "Warm?" "Yes, but not too warm"

	Time	Blood Pressure	Respiration	Pulse Rate	Remarks
11	01 59 seconds	102/64		80	
11	02 43 seconds	102/62			Felt a tingling in the jaws —just an itching back there, that was all
		Injection finished			
11	03 14 seconds	102/62		80	
		Patient did not complain of a headache but said that he would like a hypodermic injection into the muscle because "you usually get one when you get it in the vein like this, and it goes so slow" He denied that he had a headache now, however			

## COMMENT AND LITERATURE

We have demonstrated in the foregoing experiments that in the addicts who acted as subjects morphine was tolerated in far greater amounts than those required to prevent withdrawal symptoms. The intramuscular dosages were three, four and six times the amounts usually given, while the intravenous dosages were six, seven and nine times the usual quantities. In the two cases in which the regular dosage was abruptly withdrawn for a period of forty-eight hours, the tolerance for intravenous doses was still present, in one case 20 grains (1.3 Gm.) being administered in fifty-six minutes and in the other 11 grains (0.7 Gm.) in one hour and sixteen minutes. These additional quantities did not prolong the period before the addict again requested his drug. This is contrary to the statement of Bishop,<sup>2</sup> who claimed that additional quantities prolonged proportionately the interval between demands for the drug.

The physiologic changes brought about by these additional amounts taken as a whole may be regarded as practically negative. In case 26-21, there was an increase in the venous oxygen of the blood drawn from the median basilic vein following administration of these large quantities compared to that present while the addict was receiving his regular dosage and also following the abrupt withdrawal period. All the intravenous experiments were accompanied by a distinct flushing of the face, neck and upper part of the chest anteriorly. All the addicts complained of feeling more or less warm, as well as "loaded." Careful studies of the blood pressure and pulse rates did not reveal any essential differences accompanying the sensations described by the addict.

The question naturally follows, "What has become of this additional morphine and why has it been ineffective in producing any pronounced physiologic changes?" Failure of absorption cannot be considered, as in

<sup>2</sup> Bishop, Ernest S. *The Narcotic Drug Problem*, New York, The Macmillan Company, 1921, p. 33.

five experiments the drug was given intravenously most of it having left the circulation at the conclusion of the injections, as Dr. Balls was able to find less than 1 mg. in 25 cc. of blood. Failure to bring about any obvious changes in the respiration and the absence of any tendency to sleep on the part of the addicts prove the ineffectiveness of these large doses in bringing about the normal pharmacologic action of morphine on the central nervous system. Several conclusions are to be considered in this respect. First, the additional amounts have no effect on the central nervous system, the latter having become tolerant to large as well as to small amounts, second, the additional amounts must be either rapidly excreted or removed from the blood by tissues other than those of the central nervous system and destroyed, or chemically bound and made inert, and slowly returned to the blood for excretion. The latter conclusion is that of Terruchi and Kai,<sup>3</sup> who worked with rabbits.

Faust<sup>4</sup> attributed tolerance in dogs addicted to morphine to a mechanism developed in them which rapidly destroyed the morphine, as he was unable to recover any in their feces. Rubsamen<sup>5</sup> agreed with Faust that there was increased destruction but was able to recover sufficient morphine from tolerant rats to kill nontolerant rats. Rubsamen concluded, then, that there must be not only an increased destruction but also an increased tolerance on the part of the central nervous system. Terruchi and Kai<sup>3</sup> recovered quantities of morphine from the muscles and small amounts from the liver and brain of addicted rabbits. In their conclusions, Terruchi and Kai stated: "We venture to conclude that the morphinism is due to the acquired power of the living organism to destroy morphine, and to excrete it besides the augmented power to reserve it in a large amount by the muscles, so that even though a large amount of it should be introduced into the body all at once it can be prevented from immediately attacking the central nervous system."

In consideration of the work just cited and our own experiments, we believe that these large amounts of morphine introduced into the circulation are promptly removed by the muscles, so that only small quantities are available for action on the central nervous system. Having once been removed by the muscles, the morphine must have been destroyed or returned slowly to the circulation in small quantities, as Dr. Balls was able to detect only the slightest amounts in the blood. The regular return of craving for the drug on the part of the addicts

3 Terruchi, Yutaka, and Kai, Sotaro. On the Fate of Morphine Which Has Been Injected into the Animal Body, *J. Pharm. & Exper. Therap.* **31** 177, 1927.

4 Faust, E. S. Ueber die Ursachen der Gewohnung an Morphin, *Arch. f. exper. Path. u. Pharmacol.* **44** 217, 1900.

5 Rubsamen, W. Experimentelle Untersuchungen über die Gewohnung an Morphin, *Arch. f. exper. Path. u. Pharmacol.* **59** 227, 1908.

within a period of three or four hours would indicate, on the other hand, a rather rapid destruction in the muscles, or a quick elimination. Using the hypothesis of Terruchi and Kai,<sup>3</sup> one can find a plausible explanation for the frequency with which the addict increases the amounts required for his need. With the development of a mechanism in the muscles for the removal of morphine from the circulation, one can conceive of it becoming so effective as to leave an insufficient quantity for action on the central nervous system and the addict consequently increasing his regular dosage.

We believe from indirect evidence and the behavior of addicts in general that the quantity of morphine required to prevent the appearance of withdrawal symptoms to be considerably less than is normally used by them. This evidence is based on the following observations. All of our patients who have taken a cure either in our ward or in other institutions and who have had a relapse always begin the use of the drug again in small quantities, rarely more than from  $\frac{1}{4}$  to  $\frac{1}{2}$  grain (0.01 to 0.03 Gm.) at each injection. These amounts are ample to restore them to what they consider their normal feeling and also to give them the so-called "kick." These amounts suffice for various lengths of time, and as soon as the "kick" is no longer obtained the addict begins increasing the amounts taken. Our experience with reducing the doses results in little complaint on the part of the patient regardless of the amounts being used or the speed of reduction until the point is reached where the individual dosages are reduced from  $\frac{1}{2}$  grain to lower amounts. It is at this point that the addict becomes exceedingly difficult to handle and presents withdrawal symptoms.

Another phase in this problem of the amounts required to prevent withdrawal symptoms is the existence of two more or less ill defined groups of addicts which they themselves classify as "users" and "hogs." One also encounters two mental states following the use of morphine in which the addicts say that they feel "normal" or that they feel "loaded." The group of so-called "users" are able to get along nicely over a period of years on small daily dosages, but nevertheless require these small dosages to prevent withdrawal symptoms. The other group consists of those who are not content to feel normal but who are constantly desirous of being "loaded," and it is the persons in this group who continually increase the amounts taken and are forced to take a cure, after which they are able to begin all over again with small amounts.

Our experience with addicts and all cures, including "cold turkey,"<sup>6</sup> is that at the end of the week to ten days all acute withdrawal symptoms have disappeared. The addict is now able to satisfy his craving as well as to derive a "kick" with dosages as low as from  $\frac{1}{8}$  to  $\frac{1}{4}$  grain (8 to 16 mg.)

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6 Abrupt withdrawal without the substitution of any drug

If ignorant of this small requirement, the addict may take his regular dosage and suffer serious results and even death. One of our patients died suddenly following discharge from the hospital after taking an injection of the same quantity used before the cure was taken. These sudden deaths are not infrequent, according to addicts, although the reliability of their statements must always be questioned.

It would appear, then, on the basis of the conclusions of Terriuchi and Kai that within a week or ten days the muscles lose their ability to remove the drug from the circulation, and that small quantities will again suffice to give the addicts their feeling of normality or "kick." Furthermore, the foregoing theory still being used as an explanation, the ability of the muscles to remove the morphine from the circulation is not brought into play until dosages in excess of those required to prevent withdrawal symptoms are used.

This application of the theory of Terriuchi and Kai does not, however, offer any explanation as to the cause of the appearance of the withdrawal symptoms nor the presence of the craving for the drug after the acute withdrawal symptoms have disappeared. Marme<sup>7</sup> attributed the cause of the withdrawal symptoms to the presence of pseudomorphine and believed that additional amounts of morphine were required to counteract the presence of the pseudomorphine. This work has been criticized by Donath,<sup>8</sup> Stark,<sup>9</sup> Marquis,<sup>10</sup> Toth<sup>11</sup> and Gioffredi,<sup>12</sup> in a review of the literature on tolerance and withdrawal phenomena by Du Mez.<sup>13</sup> Before accepting any explanations or theories as to what has happened to the morphine, one should know whether these large quantities are rapidly excreted in human addicts, by what channels, and whether morphine is still being excreted while withdrawal symptoms are present. Such experiments are planned and will be carried out as our next step in the study of opium addiction.

7 Marme, W. Untersuchungen zur acuten und chronischen Morphin-Vergiftung, *Deutsche med. Wchnschr.* **9** 197, 1883.

8 Donath, J. Das Schicksal des Morphins im Organismus, *Arch. f. d. ges. Physiol.* **38** 528, 1886.

9 Stark, E. Untersuchungen über die Gewöhnung des thierischen Organismus an Gifte, *Inaug. Diss.*, Erlangen, 1887, cited by Faust, *Arch. f. exper. Path. u. Pharmacol.* **44** 225, 1900.

10 Marquis, E. P. Ueber den Verbleib des Morphins im thierischen Organismus *Pharm. Ztschr. f. Russland* **35** 549, 1896.

11 Toth, L. Bemerkungen zur Erklärung der chronischen Morphinimmunität, *Schmidt's Jahrb.*, 1891, vol. 229, p. 135.

12 Gioffredi, Carlo. Recherches ultérieures sur l'immunsation pour la morphine, *Arch. ital. de biol.* **31** 398, 1899.

13 Du Mez, A. G. Increased Tolerance and Withdrawal Phenomena in Chronic Morphism, *J. A. M. A.* **72** 1059 (April 12) 1919.

## CONCLUSIONS

The intramuscular injection of morphine sulphate in dosages of three, four and six times the usual amounts given, and the intravenous injection of dosages six, seven and nine times the amounts usually given to the human opium addicts who acted as subjects resulted in insignificant changes in the pulse and respiration rates, electrocardiogram, chemical studies of the blood, and the behavior of the addict

The intravenous administration of 20 grains and 11 grains to two different addicts following a forty-eight hour withdrawal period also failed to produce any significant physiologic changes or changes in behavior after fifty-six minutes and one hour and sixteen minutes, respectively

Analyses of the blood for morphine showed the presence of less than 1 mg per 25 cc of blood, indicating its rapid removal following the completion of the injection

# THE ARTERIOLES IN CASES OF HYPERTENSION \*

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For the last sixty years many have studied the histologic changes in the smaller arteries in diffuse disease of the vascular system. There has been considerable controversy as to whether any characteristic pathologic lesion is present. Our interest in this subject was renewed when the ophthalmologist was so frequently able to demonstrate narrowing of the retinal arteries and arterioles in cases of malignant hypertension. A year ago Keith, Wagener and Kernohan<sup>1</sup> were able to show in such a case that there were common features in the smaller arteries and arterioles in many organs, including those supplying the voluntary muscle. The latter observation suggested that biopsy material from a superficial muscle in ambulatory cases of hypertension might show early histologic changes in the smaller arteries. Muscle tissue was chosen because it composes about 35 to 40 per cent of the body and thus an assumption that there is a widespread lesion of the arterioles could be readily proved or disproved.

## LITERATURE

The pertinent literature of the last sixty years has been reviewed. In 1868, Johnson<sup>2</sup> systematically studied the smaller arteries of most of the tissues in cases of chronic Bright's disease. He demonstrated thickening of the media, or muscular coat, and concluded that there was an arterial hypermyotrophy similar in cause to the hypertrophy of the heart muscle. Gull and Sutton<sup>3</sup> were unable to find such thickening of the media, and in 1872 they concluded, from their studies of similar cases,

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<sup>1</sup> From the Section on Pathologic Anatomy and the Division of Medicine, the Mayo Clinic

1 Keith, N M, Wagener, H P, and Kernohan J W. The Syndrome of Malignant Hypertension, *Arch Int Med* **41** 141 (Feb) 1928

2 Johnson, George. On Certain Points in the Anatomy and Pathology of Bright's Disease of the Kidney. II. On the Influence of the Minute Blood-Vessels upon the Circulation, *Tr Medico-Chir Soc London* **51** 57, 1868

3 Gull W W and Sutton, H G. On the Pathology of the Morbid State Commonly Called "Chronic Bright's Disease with Contracted Kidney," *Tr Medico-Chir Soc London* **55** 273, 1872



that the lesion in the smaller arteries was of a hyaline, fibroid, degenerative type. Five years later, Ewald<sup>4</sup> investigated a large series of these cases, and his observations confirmed the presence of hypertrophy of the media first described by Johnson. He particularly called attention to the increased thickness of the walls of the vessels and the narrowed lumen. It should be pointed out, however, that this early work was done before the present histologic technic was devised, therefore, it is difficult to draw definite conclusions from it.

Using modern histologic technic in a large series of such cases, Jores,<sup>5</sup> in 1904, carried out a thorough and comprehensive study of the small visceral arteries. The specific vascular change which he observed was characterized by degenerative processes in the intima, hyaline and fatty changes, and a hyperplastic thickening of the internal elastic membrane. He noted also that this lesion was more frequently found in the small arteries of the kidney, the spleen and the pancreas, and he specifically stated that when the lesion was widespread in many different organs he was unable to demonstrate it in the skeletal muscle. Jores considered it possible that hypertrophy of the muscular coat sometimes occurs, but that this hypertrophy is not specific or prominent and that it may be due to postmortem contraction. In contrast to these generalizations, it is significant that he mentioned the case of a young man, aged 24, with aortic insufficiency due to rheumatic endocarditis, in whom there was definite thickening of the muscle of the media of the arterioles in many organs, including arterioles of the skeletal muscle. He also noted that in this case the thickness of the wall was considerably increased in relation to the diameter of the lumen. Omission of a reading of the blood pressure in this case is regrettable, even though the case occurred before clinical determinations of the blood pressure were made as a routine. Jores' statement has been generally accepted, that when there is a diffuse lesion of the arterioles, it is chiefly of a degenerative nature and is limited to the intima. In 1910, Fischer and Schlayer<sup>6</sup> noted that peripheral arteries, which on palpation seemed thickened, when examined histologically frequently did not show any intimal change. They stressed the absence of intimal change and suggested that although hypertrophy of the media is difficult to demonstrate, it is sometimes present, and may be of

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4 Ewald, C. A. Ueber die Veränderungen kleiner Gefässe bei Morbus brightii und die darauf bezüglichen Theorien, *Virchows Arch f path Anat* **71** 453, 1877.

5 Jores, L. Ueber die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis, *Virchows Arch f path Anat* **178** 367, 1904.

6 Fischer, Heinrich, and Schlayer. Arteriosklerose und Fühlbarkeit der Arterienwand, *Deutsches Arch f klin Med* **98** 164, 1910.

great significance in early arterial disturbances Fahr<sup>7</sup> and Herxheimer<sup>8</sup> noted that the lesion described by Jones was chiefly limited to the renal arterioles and was not widespread in arterioles of other organs Fahr,<sup>9</sup> in 1916, described a series of cases in which changes in the renal arterioles were marked, with thickening and even necrosis of the vascular walls, these secondarily caused distinct changes in the renal parenchyma He termed the condition malignant renal sclerosis, since renal insufficiency was present and the prognosis was unfavorable Fahr, in 1919 and 1920, emphasized the special features of the lesion and intimated the possibility of a toxic etiologic factor He also pointed out that the lesion usually occurred in persons aged less than 50, whereas senile arteriosclerotic changes were most common in older persons Both Herxheimer<sup>10</sup> and Stein<sup>11</sup> reported cases of malignant sclerosis of the renal vessels, with changes in the renal arterioles, as described by Fahr However, they did not wholly accept his theory as to a possible toxic causative agent In two long, comprehensive articles, in 1922 and 1925, Fahr<sup>12</sup> discussed his observations in a series that included cases of benign and cases of malignant sclerosis He again stated that the arterioles of organs other than the kidney and particularly those of the skeletal muscle, the skin and the intestine are relatively free from arteriosclerotic degenerative changes He did note that in the arterioles of the skin, the intestine and especially the skeletal muscle, the media is well developed, contrary to the condition in the renal arterioles, in which the media is reduced Fahr concluded that malignant renal sclerosis develops as a result of parasitic or chemical poisons, causing a "necrotizing arteriolitis," whereas benign sclerosis results from wear and tear, giving rise to a degenerative type of sclerosis He believed that the constant hypertension in both groups is of renal origin

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7 Fahr, T Zur pathologisch-anatomischen Unterscheidung der Schrumpfniern nebst Bemerkungen zur Arteriosklerose der kleinen Organarterien, Frankfurt Ztschr f Path **9** 15, 1912

8 Herxheimer, Gotthold Niere und Hypertonie, Verhandl d deutsch path Gesellsch **15** 211, 1912

9 Fahr, T Ueber maligne Nierensklerose (Kombinationsform), Centralbl f allg Path u path Anat **27** 481, 1916

10 Herxheimer, Gotthold Ueber Arteriolonekrose der Nieren, Virchows Arch f path Anat **251** 709, 1924

11 Stern, Max Ueber einen besonders akut verlaufenen Fall von Arteriolonekrose der Nieren mit dem makroskopischen Bilde der "Grossen bunten Niere," Virchows Arch f path Anat **251** 718, 1924

12 Fahr, T Ueber die Beziehungen von Arteriolensklerose, Hypertonie und Herzhypertrophie, Virchows Arch f path Anat **239** 41, 1922, Henke, F, and Lubarsch, O Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol 6, pt 1, p 121

Evans<sup>13</sup> investigated the lesions in the arteries and arterioles of many organs in a large series of cases. The tissues examined were removed during operation or at necropsy. The ages of the patients varied from 8 to 86 years. In cases with hypertension and cardiac hypertrophy, he invariably demonstrated the characteristic changes of diffuse hyperplastic sclerosis in many arterioles. The criteria on which he made a diagnosis of this lesion were (1) proliferation and then degeneration of the intima, (2) thickening of the media due to hypertrophy of the muscle, with lack of evidence of any degenerative changes in this layer. The organs the arterioles of which usually showed this change were the kidney and the spleen. The change occasionally was present elsewhere in lesser degree, but practically never in heart or skeletal muscle. Evans believed that his observations indicate that diffuse hyperplastic sclerosis of the arterioles is similar in children and in adults, that it can be distinguished from senile arteriosclerosis, that it is probably inflammatory and that the diffuse arteriolar and renal lesions are the simultaneous results of a single pathogenic agent.

Fishberg<sup>14</sup> made a similar study in a large series of cases of essential hypertension. Like Jores, Fahr and Evans, he found that atrophy of the media was the rule, and that rarely were there any noticeable changes in the arterioles of voluntary muscle. Similar negative observations were made in the arterioles of voluntary muscle by Branch and Linder<sup>15</sup> in six cases of chronic glomerulonephritis occurring in young persons. Fishberg<sup>16</sup> did find hypertrophy of the media in the renal arterioles, but not elsewhere in certain cases of chronic glomerulonephritis. Brogsitter<sup>17</sup> examined the mesenteric vessels in thirty-three cases of hypertension. He found thickening of the media in some cases, with the muscle layer rich in nuclei, changes which he interpreted as being the result of maximal contraction. He did not find any relationship between the height and the duration of the hypertension and the changes in the mesenteric arteries. Michel,<sup>18</sup> in 1884, in an ophthalmoscopic

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13 Evans, Geoffrey. A Contribution to the Study of Arterio-Sclerosis with Special Reference to Its Relation to Chronic Renal Disease, *Quart J Med* **14** 215, 1920-1921, Arteriosclerosis in Children, *ibid* **16** 33, 1922-1923.

14 Fishberg, A. M. Anatomic Findings in Essential Hypertension, *Arch Int Med* **35** 650 (May) 1925.

15 Branch, Arnold, and Linder, G. C. The Association of Generalized Arteriolar Sclerosis with High Blood Pressure and Cardiac Hypertrophy in Chronic Nephritis, *J Clin Investigation* **3** 299, 1926.

16 Fishberg, A. M. Arteriolar Lesions of Glomerulonephritis, *Arch Int Med* **40** 80 (July) 1927.

17 Brogsitter, A. M. Zur Anatomie der Splanchnikusgefasse beim Hochdruck, *Munchen med Wchnschr* **2** 1049, 1924.

18 Michel, Julius. *Lehrbuch der Augenheilkunde*, Wiesbaden, J. F. Bergmann, 1884.

study of the retina in patients with general arteriosclerosis and nephritis noted the presence of sclerosis of the retinal arteries. Karl,<sup>19</sup> in 1887, described this sclerosis in the retinal and choroidal arteries as the primary pathologic basis of "albuminuric retinitis." He found, histologically, arteritis of the retinal and choroidal arteries, which terminated in hyaline thickening and degeneration of all the coats. Gunn,<sup>20</sup> in 1898, noted in cases of general arteriosclerosis the uniform constriction of the retinal arteries and the ischemic features of the frequently associated retinitis. Coats<sup>21</sup> showed that the histologic basis of this apparent constriction of the retinal arteries was an increase of the fibrous tissue in the media and the adventitia. Only rarely was there proliferation of the endothelium. Leber,<sup>22</sup> in 1915, observed, in cases of retinitis of nephritis, hypertrophy of the muscular coat of the central retinal and posterior ciliary arteries. He considered that the ophthalmoscopic evidence of retinal arteriosclerosis, in the absence of retinitis, was due to endarteritis with subendothelial intimal proliferation. He also suggested that in some cases the appearance of the arteries might be due to tonic contraction without demonstrable histologic changes. Volhard,<sup>23</sup> in 1921, emphasized the angiospastic features of "albuminuric retinitis" in chronic glomerulonephritis and in malignant renal sclerosis. Cohen<sup>24</sup> found, histologically, marked thickening of the vessels in the choroid and the retina of patients with diffuse vascular disease. Keith, Wagener and Kernohan,<sup>1</sup> in their study of the syndrome of malignant hypertension, emphasized the presence of a lesion in the arterioles throughout the body. This lesion was observed during life in the retina and histologically in both the retina and the choroid. The characteristics of this lesion were the same in the different tissues examined, which included all the important organs of the body. The three anatomic divisions of the walls of the arterioles were thickened or hypertrophied, especially the intima and the media, with an almost total absence of signs of degeneration.

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19 Karl, Herzog, in Bayern. Ein Beitrag zur pathologischen Anatomie des Auges bei Nierenleiden, Wiesbaden, J. F. Bergman, 1887.

20 Gunn, Marcus. On Ophthalmoscopic Evidence of General Arterial Disease, *Tr. Ophth. Soc. U. Kingdom* **18** 356, 1898.

21 Coats, George. Intraocular Vascular Disease, *Ophthalmoscope* **4** 605, 1906.

22 Leber, T. Die Krankheiten und Anomalien des Blutgefäß-Systeme der Netzhaut, in Graefe-Saemisch. *Handbuch der gesamten Augenheilkunde*, Leipzig, Engelmann, 1915, vol. 2, p. 101.

23 Volhard, F. Ueber die Retinitis albuminurica, *Verhandl. d. Kong. f. inn. Med.* **33** 422, 1921.

24 Cohen, Martin. Significance of Pathologic Changes in Fundus in General Arterial and Kidney Diseases, *J. A. M. A.* **78** 1694 (June 3) 1922.

## CLINICAL OBSERVATIONS

Hypertension has been classified as benign and malignant with the retinal picture as one of the most significant diagnostic points in the latter. However, there is a group of cases of hypertension in which it is difficult to make such a differentiation. In this study, we have grouped these intermediate cases as those of severe benign or early malignant hypertension.<sup>25</sup> Fifty-three cases were studied and biopsy was done, eleven cases were diagnosed as benign, eighteen as severe benign or early malignant, and twenty-three as malignant hypertension. The remaining case, one of chronic glomerulonephritis, was studied for comparison with the cases of diffuse vascular hypertensive disease. Complete vascular and renal studies were made in the hospital in most of the cases, and at the same time the biopsy was done. The clinical data will be found in detail in table 1.

*Benign Hypertension*—In this group, the longest duration of known hypertension was fifteen years, in other cases, the patients did not know that they had hypertension until it was discovered on examination in the clinic. The average duration was five years and eight months. The ages varied from 30 to 65 years, with the average at 47 years. The following are abstracts of illustrative cases.

CASE 10—A physician, aged 30, discovered in himself eight years before admission a blood pressure of 140 systolic and 100 diastolic and symptoms of palpitation and heart consciousness. He was in good physical condition when he came to the clinic in October, 1928. The blood pressure varied from 155 to 180 systolic, and from 120 to 125 diastolic. There was mild cardiac hypertrophy, peripheral arterial sclerosis grades 1 to 2, no retinitis and slight retinal sclerosis. The blood urea was normal. The urine was clear, except for a trace of albumin. The electrocardiographic report did not reveal anything significant.

CASE 6—A man, aged 51, was first seen in April, 1927, at this time his chief complaint was nervousness. The systolic blood pressure was 200 and the diastolic 130 on first examination. Later it was 120 systolic and 85 diastolic. A diagnosis of benign hypertension, migraine and vasomotor instability was made. He returned for reexamination in August, 1927, at this time the blood pressure varied from 190 to 140 systolic and from 125 to 90 diastolic. On his last visit, in May, 1928, he complained of dizzy spells, his blood pressure was 210 systolic and 115 diastolic. On later examination, it was 110 systolic and 90 diastolic.

The general examination was essentially negative, except for nervous instability. The heart was slightly enlarged and there was mild sclerosis of the peripheral and retinal vessels. The blood count and urinalysis did not reveal anything abnormal. The renal function was satisfactory. The electrocardiogram was negative. Examination of the peripheral capillaries at the nailfold disclosed mild contraction with slightly increased mechanical flow. A recent communication from the patient stated that he was in good condition and was working daily.

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<sup>25</sup> Adams and Brown (Considerations on the Treatment of Essential Hypertension, *Ann Clin Med* 5 1036, 1927) studied a similar group of cases. Many of the present series are distinguished from theirs in that retinal, renal and cardiac functions often were well maintained at the time of examination.

CASE 3—A woman, aged 38, came to the clinic on May 2, 1928, complaining of high blood pressure and of headaches of one and a half years' duration. She had been married ten years and had two children, 8 and 6 years of age. The blood pressure had been normal during pregnancy and albuminuria had not occurred. In the course of the third pregnancy, in December, 1926, she had become unconscious and had been blind for two or three weeks. The blood pressure then had been found to be 230 systolic and albuminuria had been present. She had been sent to a hospital and the pregnancy had been terminated. Since then she had had constant headache, some decrease in vision and slight dyspnea.

General examination at the clinic revealed a well developed and well nourished woman with a blood pressure varying from 220 to 140 systolic and from 130 to 95 diastolic. The heart was normal in size and there was only slight peripheral arterial sclerosis. The arteries of the retina were markedly contracted, with sclerosis, grades 1 to 2. There were questionable signs of healed retinitis. Examination of the blood and the urine did not reveal anything abnormal and renal function was satisfactory. The electrocardiogram was negative. The capillaries at the nailfold were moderately contracted and flow was swift.

*Severe Benign or Early Malignant Hypertension (Intermediate Group)*—In this group, the duration of known hypertension varied from fifteen years to two months, with an average of four years. The variation in age was from 21 to 59 years and the average was 47 years. The following are abstracts of illustrative cases.

CASE 15—A woman, aged 23, registered at the clinic in May, 1928, complaining of headaches that had been recurring since November, 1927. At the time of the onset, her college physician had noted tachycardia with a rate of 110, which was reduced by digitalis to 80. Hypertension also was found and was treated with salts and Turkish baths.

The general examination was negative except for slight cardiac hypertrophy. The blood pressure varied from 205 to 140 systolic and from 160 to 100 diastolic. There was retinal sclerosis, grade 1, but peripheral sclerosis or retinitis was not present. The blood and the urine did not reveal anything abnormal and the renal function was satisfactory. The electrocardiogram was negative. There was mild contraction with moderate tortuosity of the capillaries at the nailfold, and there was fast mechanical flow. A recent communication from the patient stated that she was working regularly every day.

CASE 28—A man, aged 22, was last seen at the clinic in November, 1927. In January, 1927, he had come to the clinic complaining of headaches that had been recurring during the past two years. He had passed an examination for life insurance in 1924. The blood pressure in September, 1926, had been 220 systolic. The blood pressure in January, 1927, had been 230 systolic and 150 diastolic. A diagnosis was made of essential hypertension (pre-malignant) and generalized arteriosclerosis. In November, 1927, the blood pressure was 245 systolic and 140 diastolic. Later it was 155 systolic and 105 diastolic.

There was mild cardiac hypertrophy with peripheral sclerosis, grade 2. There was no retinitis, the retinal arteries were mildly sclerosed. The blood count was normal, and the renal function was satisfactory. Electrocardiographic observations did not indicate any abnormality. The capillaries at the nailfold were mildly contracted and tortuous, and flow was swift.

TABLE 1—Results of Vascular and Renal Studies and Biopsy Made on Persons with Hypertension

Case	Hypertension	Sex	Age	Blood Pressure				Cardiac Hypertrophy*	Peripheral Sclerosis *	Blood			Urine		Electrocardiogram	Tortuosity *	Flow (M Denotes Mechanical) *	Contraction *					
				Systolic	Diastolic	Maxi- mum	Mini- mum			Ratio of Wall to Lumen of Artery	Hemoglobin, Cent (Dare)	Erythrocytes, Mil	Urea, Mlg per 100 Cc	Maximum					Specific Gravity	Albumin *	Phenolphthalein per Cent		
1	Benign	M	44	235	145	180	90	1	2+	3	1.130	60	3.22	48	1.016	1.004	2	35	Inverted T wave leads I and II	2	2	1	
2	Benign	F	55	240	120	140	80	§	1	1	1.120	70	4.51	26	1.030	1.001	4	60	Diphase T wave lead I	0	3M	1+	
3	Benign	F	38	220	130	140	95	0	§	1+	1.140	68	4.08	18	1.010		0	75	Essentially negative	0	3	2	
4	Benign	M	50	210	140	150	95	2	2	0	1	1.14**	70	4.60	34	1.026		0	85	Essentially negative	0	1	2
5	Benign	M	42	210	140	130	75	1	3	3	1.112	76	4.31	24	1.025	1.002	2	75	Inverted T wave leads I and II	0	0	§	
6	Benign	M	51	210	115	110	90	1	1+	0	1	1.118	79	4.88	25	1.025	1.001	0	70	Essentially negative	0	1M	1
7	Benign	M	57	200	120	130	70	1	2+	0	§	1.115	79	4.94	30	1.027	1.002	0	50	Diphase T wave leads II and III	2	2M	1
8	Benign	M	63	180	100	140	90	1+	1+	0	1	1.126	77	4.05	40	1.020	1.002	0	45	Essentially negative	1+	2	0
9	Benign	M	41	180	130	140	90	1	2+	0	1	1.113	77	4.65	32	1.027	1.003	2	75	Essentially negative	0	2	1
10	Benign	M	30	180	125	155	120	1	1+	0	§	1.117	71	4.66	26	1.028		1	85	Inverted T wave lead III			
11	Benign	F	41	200	125	125	70	§	2	2	3	1.115	71	3.98	35	1.010	1.003	3	35	Inverted T wave lead I	1	0	0
12	Severe benign	M	54	200	140	130	80	1	1+	2	1.111	73		33	1.026	1.003	0	50	Diphase T wave lead I				
13	Severe benign	M	22	200	140	135	90	§	§	0	1	1.116	80	4.45	28	1.025	1.002	2	40	Essentially negative			
14	Severe benign	M	59	185	115	130	70	2	2+	0	3	1.08	78	4.53	38	1.032		0	40	Inverted T wave leads II and III	1	2	1
15	Severe benign	F	23	205	160	140	100	§	0	0	1	1.105	75	4.72	15	1.028	1.001	0	75	Essentially negative	2	2M	1
16	Severe benign	F	39	250	140	190	105	1	1	1	1.112	71	4.30	20	1.030		2	55	Inverted T wave leads I and II Diphase T wave lead III				
17	Severe benign	M	39	190	140	125	100	1	1+	2	1	1.110	76	4.90	36	1.015	1.003	2	40	Inverted T wave leads I and II			
18	Severe benign	M	21	190	140	150	100	2	2	0	1	1.106	78	4.99	28	1.023	1.002	2	40	Inverted T wave lead I Diphase T wave lead II	1	2M	2
19	Severe benign	F	38	240	160	150	110	1	§	0	1+	1.114	78	4.76	30	1.030	1.001	2	25	Essentially negative			
20	Severe benign	M	42	230	155	175	130	1	2+	3	3	1.112	74	4.04	54	1.016	1.003	2	30	Inverted T wave leads I and II	1	2	1
21	Severe benign	M	57	280	140	170	90	3	3	3	3	1.117	70	4.71	45	1.026		3	40	Inverted T wave leads I and II Slurred T wave lead III	1+	2	1+
22	Severe benign	M	54	270	140	160	100	1+	2+	1	2+	1.113	78	4.20	27	1.030	1.001	0	60	Essentially negative			
23	Severe benign	F	23	225	160	175	110	1	2	1	1+	1.112	75	4.10	37	1.021	1.003	4	60	Inverted T wave leads I and II	1	2	
24	Severe benign	M	48	200	130	160	80	2	2+	1	1+	1.112	75	4.11	38	1.020	1.002	2	25	Auricular premature contraction	0	2	1
25	Severe benign	M	51	225	140	175	110	1	2	1	2	1.111	68	4.46	30	1.010			65	Essentially negative	1	3M	1

26	Severe benign	M	37	255	155	170	110	1	1	0	1+	1 1 07	75	4 66	36	1 022	1 003	2	55	Inverted T wave lead I Diphase T wave lead II	0	3M	2
27	Severe benign	F	56	260	160	165	100	1	1+	1	2	1 1 4	73	4 22	38	1 022	1 002	3	50	Inverted T wave leads I, II and III	0	2	2
28	Severe benign	M	22	245	140	155	105	1	2	0	1	1 1 05	80	4 79	22	1 010		0	85	Essentially negative	1	2	1
29	Severe benign	M	48	240	160	175	110	1	2	0	1	1 1 20	77	4 74	23	1 018	1 003	3	50	Inverted T wave leads I and II	0	2M	1
30	Malignant	M	52	240	150	210	110	2	3	3	3	1 1 09	60	3 64	133	1 010	1 007	3	2	Inverted T wave leads I and III	2	2	1
31	Malignant	M	45	235	160	195	120	2	3	1	3	1 1 30	77	4 44	37	1 021		2	35	Inverted T wave leads I and II	1	3	3
32	Malignant	M	34	245	145	175	120	2	1	2	3	1 1 20	72	4 88	34	1 024	1 001	2	35	Inverted T wave leads I and II	0	2	1
33	Malignant	M	26	220	170	170	130	1+	1+	3	2	1 1 2	80	4 57	41	1 025	1 002	3	45	Inverted T wave leads I and II	0	3	2
34	Malignant	M	50	320	175	170	80	1+	2	1	2	1 1 1	77	5 02	30	1 024	1 003	4	35	Diphase T wave leads I and II Inverted T wave lead III	2	3	3
35	Malignant	M	55	270	170	180	110	1	2+	2	2	1 1 2	60	3 90	38	1 014	1 002	2	45	Inverted T wave lead I	1	3M	0
36	Malignant	M	55	220	140	155	105	1	2+	2+	3	1 1 2	75	4 80	64	1 020	1 003	2	25	Essentially negative	1	2M	0
37	Malignant	M	54	230	140	160	100	1	2+	2	2+	1 1 3	80	4 26	38	1 023		2	35	Essentially negative	1	2	1
38†	Malignant	F	8	210	145	150	120	1	1	1	2	1 1 2	71	4 50	36	1 020	1 004	2	70	Not taken	2	2	2
39	Malignant	M	51	235	165	200	110	2	2+	2	2+	1 1 1	72	4 44	34	1 015		2	40	Inverted T wave lead I	0	3M	2
40†	Malignant	M	23	200	145	180	140	1	1+	2	1	1 1 2	80	4 96	22	1 020		0	50	Inverted T wave leads I and II Coronary T wave leads I and II	2	2	2
41	Malignant	M	42	230	145	145	110	1+	2	2	2	1 1 05	82	4 84	34	1 025	1 002	2	60	Diphase T wave lead I Inverted T wave leads I and III	0	0	1
42	Malignant	M	55	255	150	200	110	2	2	2	3	1 1 3	75	4 44	41	1 019	1 002	1	30	Inverted T wave leads I, II and III	1	2M	2
43	Malignant	M	48	290	150	190	100	2	2+	1	2+	1 1 0	85	4 16	35	1 019	1 003	2	30	Essentially negative	0	3M	0
44	Malignant	M	38	260	160	190	125	2+	2	2	3	1 1 2	78	4 53	53	1 015	1 003	2	25	Inverted T wave leads I and II	1	3M	0
45	Malignant	F	34	165	110	120	80	§	1	2	?	1 1 2	75	4 38	24	1 035	1 002	0	70	Essentially negative	2	2	2
46	Malignant	M	48	220	165	160	110	1	3	2	3	1 1 0	73	4 27	60	1 020	1 010	3	30	Inverted T wave leads I and II	0	3M	2
47	Malignant	M	58	230	140	160	80	2	2	2	2	1 1 4	44	3 06	97	1 013	1 002	3	10	Inverted T wave leads I, II and III	0	3M	2
48	Malignant	M	49	220	130	160	110	1	3	?	3+	1 1 1	72	4 30	30	1 024	1 002	0	40	Diphase T wave lead I	0	3M	2
49	Malignant	M	49	260	180	155	110	1	3	3	3	1 1 0	68	3 98	49	1 017	1 002	4	45	Inverted T wave lead III	1	3M	0
50	Malignant	M	54	255	160	140	60	1	2+	2	2	1 1 0	76	4 41	40	1 010		2	35	Inverted T wave leads I and II	0	3	1
51	Malignant	M	51	260	180	210	130	1+	3	2	3	1 1 0	68	4 00	72	1 008		2	10	Inverted T wave lead I Diphase T wave lead II	1	2M	2
52	Malignant	M	19	250	160	200	135	2	2+	2	3	1 1 2	92	4 62	36	1 019		2	30	Ventricular premature contraction	0	2	1
53	Chronic glom- erulonephritis	F	46	170	100	115	70	0	§	0	§	1 1 8	67	4 30	56	1 020		4	35	Inverted T wave lead III	0	2	1

\* Graded on a basis of 1 to 4

\*\* Same ratio at second biopsy nine months later

† Case reported by Amberg, Samuel Hypertension in the Young, Am J Dis

‡ Only case in which the Wassermann reaction of the blood serum was positive

§ Slight

¶ Trace



*Malignant Hypertension*—This group showed the characteristics described in a previous paper by Keith, Wagener and Kernohan<sup>1</sup> The duration of known hypertension in some cases was seven years, in others, the patients were not aware that they had hypertension until it was discovered at the clinic The average duration of the disorder was two years and eight months The ages varied from 8 to 55 years, with an average of 45 years The following are abstracts of illustrative cases

CASE 33—A man, aged 26, entered the clinic on March 6, 1928, complaining of high blood pressure, which had been discovered in an examination for insurance one year before At that time, the systolic pressure was 200 Slight dyspnea had been present for six months and there had been nocturia and easy fatigue for three or four months There had been blurring of vision for three weeks During the year he had lost 43 pounds (19.5 Kg)

The patient appeared ill at the time of the general examination The heart was moderately hypertrophied and there was peripheral sclerosis, grade 1+ The patient's blood pressure was 220 systolic and 170 diastolic, on one occasion, and later it was 170 systolic and 130 diastolic There was retinitis, grade 3, with edema of the disks of 2 diopters, hemorrhages, exudate and incomplete macular stars in both eyes The blood count was normal There was marked albuminuria with hematuria In the phenolsulphonphthalein test of renal function there was 45 per cent return of dye in two hours The blood urea was 41 mg, and electrocardiographic tracings gave evidence of myocardial degeneration as indicated by inverted T waves in leads I and II There was moderate contraction of the capillaries at the nailfold, with swift flow The patient died at home during the first week of July, 1928, four months after leaving the clinic

CASE 45—A woman, aged 34, registered at the clinic in January, 1928 She complained of attacks of unconsciousness recurring over a period of five years They were becoming more frequent and had been associated during the previous summer with blurring of vision She had had an occasional headache Menopause had occurred at the age of 29

The patient was well nourished and well developed with a slightly enlarged heart and slight peripheral sclerosis There was retinitis, grade 2, without retinal sclerosis Renal function was normal, and the electrocardiogram appeared to be that of a normal condition Blood pressure, on admission, was 165 systolic and 110 diastolic Later, it was 120 systolic and 80 diastolic Neurologic examination did not reveal any abnormality The cerebrospinal fluid was under increased pressure More visual disturbance developed subsequently

CASE 48—A physician, aged 49, came to the clinic on May 1, 1927 While watching operations at the clinic, he noted tingling in the left arm and leg, with numbness and weakness He had had scarlet fever with nephritis at the age of 9, and at the age of 29 he had had diphtheria complicated by nephritis and edema of the ankles At the age of 44, his blood pressure, on examination for life insurance, was 180 systolic, but later it was 145 systolic, and he received a policy for \$25,000 without an increase in rates

The patient's blood pressure at the time of examination was 210 systolic On May 9, 1927, there were bilateral choked disks of 4 diopters in the right eye and of 2 diopters in the left, with hemorrhage and exudate The arteries were markedly constricted The diagnosis of retinitis of malignant hypertension was made The blood urea was 44 mg in each hundred cubic centimeters There was an inverted T wave in lead I of the electrocardiogram With rest, the blood

pressure was reduced to 170 systolic and 100 diastolic. The cerebrospinal fluid was under a pressure of 36 cm of water. The edema of the disks cleared and on May 12 there was a choked disk in the right eye of 2 + diopters, and in the left eye of 1 + diopter.

The patient returned on Feb 20, 1928, for reexamination, the blood pressure was then 220 systolic and 130 diastolic. In the electrocardiogram there was a diphaseic T wave in lead I. The optic disks were without edema and the arteries were contracted irregularly. On May 17, the blood pressure was 210 systolic and 135 diastolic. There was an inverted T wave in leads I and II in the electrocardiogram and there was sclerosis, grade 3 +, in the retinal arteries. The optic disks were flat and pale. The patient died on May 24, 1928, following a cerebral hemorrhage.

TABLE 2—*Clinical Resume and Comparison of Three Groups of Cases of Hypertension*

Points of Comparison	Benign	Severe Benign or Early Malignant	Malignant
Number of cases	11	18	23
Blood pressure, mm			
Maximal systolic	210	280	320
Maximal diastolic	145	160	180
Minimal systolic	180	185	165
Minimal diastolic	100	115	110
Systolic more than 250, per cent		28	35
Diastolic more than 140, per cent	27	89	95
Cardiac hypertrophy, per cent			
Grade 1	73	67	40
Grade 2	18	28	52
Peripheral sclerosis, per cent			
Grade 2	55	39	30
Grade 3	27	28	57
Retinal sclerosis, per cent			
Grade 1	36	33	4
Grade 2	36	45	30
Grade 3	27	22	62
Albuminuria, per cent			
Absent	45	22	13
Grade 2	27	56	57
Renal insufficiency, per cent			
Absent	73	67	17
Grade 1	27	28	57
Grade 2		5	22
Grade 3			4
No anemia, per cent	91	100	83

*Comparison of the Three Groups*—A comparison of the clinical data in the three types of hypertensive vascular disease is made in table 2. If 250 mm is taken as a level for systolic pressure and 140 mm as a level for diastolic pressure, it will be seen that in none of the cases of benign hypertension was the systolic pressure more than 250 mm, whereas in each of the other two groups the readings in practically a third of the cases were in excess of this figure. Similar results were obtained in readings of diastolic pressure. Twenty-seven per cent of the cases of benign, 89 per cent of the cases of early malignant and 95 per cent of the cases of malignant hypertension had a diastolic pressure of 140 mm or more. On measuring the size of the heart, enlargement, grade 1, was the rule in the cases of the benign group, whereas enlarge-

ment, grade 2, was slightly more common in the cases of the intermediate groups and was present in more than half of the cases of the malignant group

Peripheral arterial sclerosis, grade 2, was present in 55 per cent of the cases of benign hypertension and in 30 per cent of the cases of malignant hypertension. Grade 3 was found in 27 per cent of the cases of benign hypertension, in 28 per cent of the cases of the intermediate group, and in 57 per cent of the cases of the malignant group. When definite peripheral sclerosis is present in malignant hypertension, the vessel often feels rubbery.

On examination of the retinal vessels, sclerosis, grade 1 or 2, was present in 72 per cent of the cases of benign hypertension and in 78 per cent of the cases of the intermediate group. Sclerosis, grade 3, was present in about 25 per cent of the cases of the benign and intermediate groups and in 62 per cent of the cases of the malignant group. Albuminuria was absent in about half of the cases of benign hypertension, and was graded 2 in about a fourth of them. In the other two groups, it was graded 2 in over half of the cases.

If one considers that a return of 50 per cent or more of phenolsulphonphthalein in two hours, and that 40 mg of blood urea or less to each hundred cubic centimeters indicate satisfactory renal function, it can be seen that the benign and intermediate groups have satisfactory renal function in the greater percentage, with mild renal insufficiency in a fourth of the cases and moderate renal insufficiency in only 5 per cent of the intermediate group. The malignant group, however, shows mild renal insufficiency in more than half of the cases, moderate insufficiency in 22 per cent and marked insufficiency in 4 per cent.

If one considers 70 per cent hemoglobin (Dare) or more and 4,000,000 or more erythrocytes in each cubic millimeter as within normal limits, it can be seen that anemia is not significant in any group.

In the study of the capillaries at the nailfold, ten cases of benign, thirteen of intermediate and twenty-one of malignant hypertension were reviewed.<sup>26</sup> Straight, mildly contracted vessels and fast mechanical flow were the rule in the cases of benign hypertension. Slight tortuosity, with mild contraction and fast flow, was shown in a greater percentage of cases in the intermediate group, and mechanical flow in about half of the cases. In the malignant group, the flow was fast, with mechanical movement, in half of the cases. The latter observation agrees with our previous observations in the last named group.

Inquiry at the time of writing brought out the fact that, of the eleven patients with benign hypertension, seven were well and four were dead. One death was due to influenza and pneumonia (case 11, table 1). The

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<sup>26</sup> The nailfold capillaries were examined by G. E. Brown, according to the Lombard technic.

other three deaths had occurred in cases 1, 5 and 8 (table 1). In cases 1 and 8, myocardial degeneration was a prominent feature. In case 5, general and cerebrospinal arteriosclerosis were marked. In the eighteen cases of the intermediate group (table 1), nine of the patients were well, one had suffered an apoplectic stroke and one had lately returned for reexamination, and the picture of the fundus was that of malignant hypertension. Two patients had died. The serious prognosis in the malignant group is again evident.<sup>1</sup> Only two of the twenty-three patients observed were reported as well, two were failing and fourteen had died. Of these fourteen, eleven had died from two to six months after dismissal (average four months).

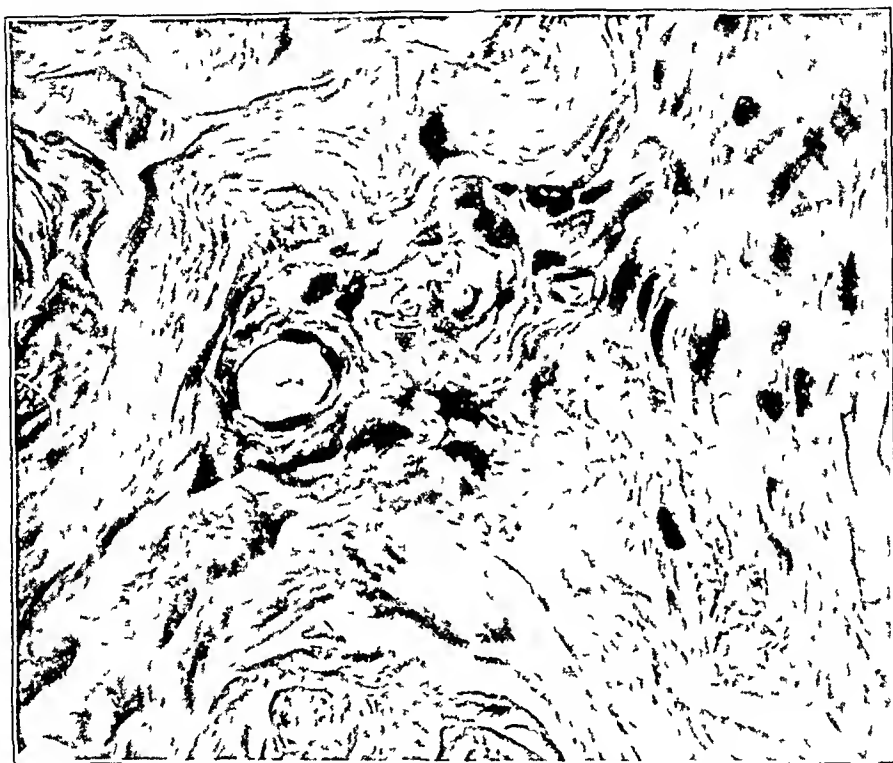


Fig 1—A normal arteriole obtained from pectoralis major muscle at necropsy. The comparatively thin wall and absence of signs of hypertrophy of media may be noted. Van Gieson stain,  $\times 600$ .

#### HISTOLOGIC STUDIES

*Biopsy*—After the injection of a local anesthetic, a small portion of the pectoralis major muscle was removed. This procedure was carried out in the fifty-three cases of the present series. Material for controls was obtained from two sources: from tissue subjacent to breasts amputated for tumors of various types in patients in whom the blood pressure was normal and at necropsy from bodies of patients whose blood pressure had not been elevated and whose hearts had not been enlarged (fig 1). In one case, a second biopsy was made nine months later and

in two cases in which biopsy was made, necropsy was performed later, and detailed studies were carried out on the arterioles in various organs. All specimens of tissue were embedded in paraffin, were cut at a thickness of 8 microns and were stained with hematoxylin and eosin, with van Gieson's and with Weigert's elastic tissue stains.

The vessels examined were the arterioles. The arteries and capillaries were not included in this study because little histologic change was seen in the capillaries of any patient with high blood pressure, and because it was difficult to obtain regularly larger arteries. We have been unable to find in the literature on anatomy actual measurements of the outside diameter of small vessels, which would permit an accurate measurable distinction between a small artery and an arteriole. Landis,<sup>27</sup> in his micro-injection studies of the blood pressure gradient in the mesentery of the frog, considered an arteriole to be from 40 to 50 microns in diameter. Many pathologists consider the afferent glomerular vessel an arteriole. We have measured a few of these vessels in the normal kidney of man and have found the outside diameter varying from 30 to 50 microns. Landis<sup>28</sup> also directly determined the fall in the blood pressure gradient in arteries, capillaries and veins in the mammalian mesentery. In some later unpublished similar experiments<sup>29</sup> in the rat and guinea-pig, he incidentally measured the diameter of certain of the vessels observed. He classified the vessels as "smallest arteries" and "arterioles" by their relation to the capillary network. The former contained a considerable number of muscle fibers and the diameter measured from 40 to 100 microns, whereas the arterioles, which arise from the smallest arteries and merge into the capillaries, contained fewer muscle fibers and were thinner, measuring from 15 to 35 microns. The diameter of the vessels measured in the present study varied from 25 to 100 microns, so that, from Landis' data, they fall into both his groups of smallest arteries and arterioles.

There were definite changes in the arterioles in many cases and also, to a slight extent, in the surrounding muscle tissue. There was a slight increase in the connective tissue around some of the arterioles and occasionally small collections of lymphocytes, which possibly were the result of the occlusion of some small arterioles. The most pronounced and most constant change observed in the vessels was in the media, which was definitely hypertrophied, and there was an increase in the nuclear elements of this tissue. There was no fibrosis or increase in connective tissue, the entire change was due to proliferation of muscle. Medial

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27 Landis, E. M. The Capillary Pressure in Frog Mesentery as Determined by Micro-Injection Methods, *Am J Physiol* **75** 548, 1925-1926.

28 Landis, E. M. Micro-Injection Studies of Capillary Pressure in Mammalian Mesentery, *Am J Physiol* **85** 387, 1928.

29 Landis, E. M. Personal communication.

to the muscular elements, the Weigert elastic tissue stain showed that there was also hypertrophy of the internal elastic lamina. In some cases, this was slightly split up, but as a general rule the splitting was not pronounced. In the intima, the change was widely varied, but the most common modification was proliferation of the lining endothelial cells. This sometimes was accompanied by proliferation of the subendothelial tissue, and when both changes were present the vessel was almost occluded. Complete occlusion of a vessel was rare, but partial occlusion was the rule. It does not seem logical to assume that any vasomotor spasm could bring about proliferation of the lining endothelial cells,



Fig 2 (case 38)—An arteriole from pectoralis major muscle obtained at biopsy from a child, aged 8. The hypertrophied musculature of the media and the proliferation of the endothelial cells of the intima may be noted. The ratio of thickness of wall to width of lumen, which normally is 1/2, is much upset here. Van Gieson stain,  $\times 350$ .

although it might possibly produce some hypertrophy of the media. Occlusion of a vessel at a higher level might possibly bring about proliferation of the lining endothelial cells even to the point of occlusion, but evidence is lacking that such occlusion existed in any of these cases. The fundamental changes occurring in these vessels were hypertrophy of the media and proliferation of the intima. There was no degenerative change, nor any change that could be attributed to senile retrogression (figs 2, 3, 4, 5, 6 and 7).

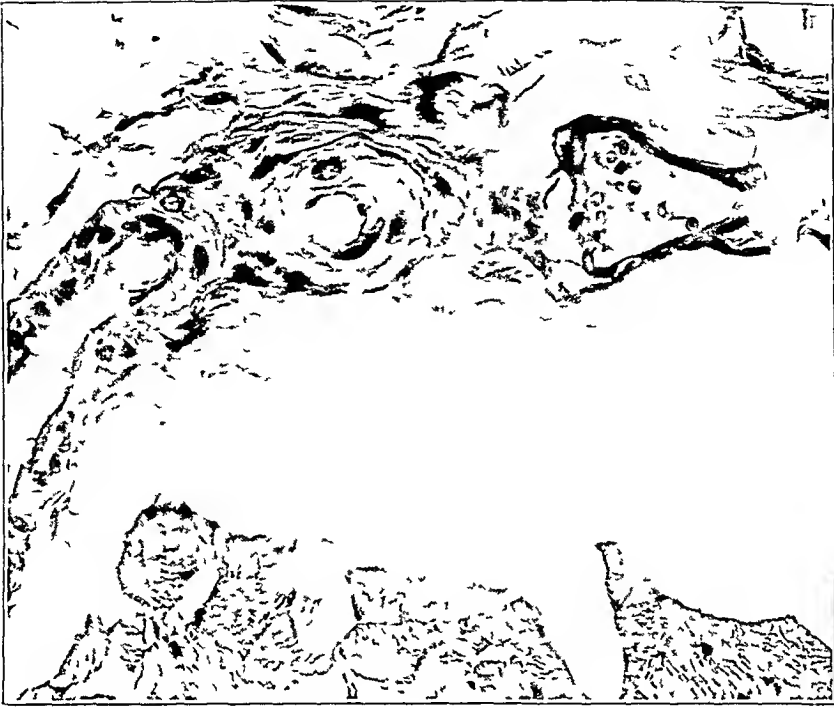


Fig 3 (case 38) —An arteriole from pectoralis major muscle obtained at biopsy, showing hypertrophied wall and narrow lumen with an upset ratio of lumen to wall Van Gieson stain,  $\times 350$

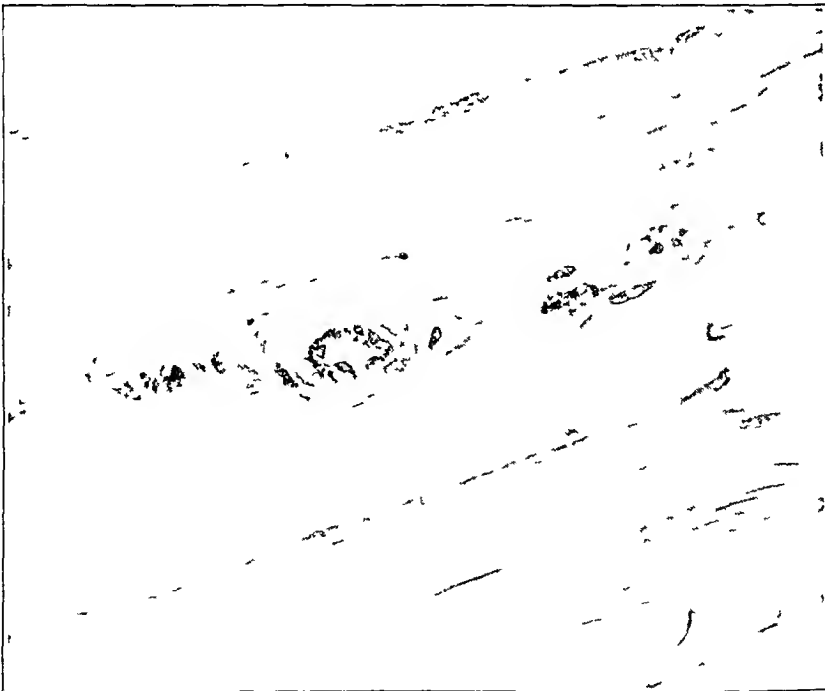


Fig 4 (case 48) —A small arteriole from pectoralis major muscle obtained at biopsy The much hypertrophied internal elastic lamina may be noted Normally, in a vessel of this size, this elastic lamina is extremely slight The vessel is 29 microns in diameter Weigert elastic stain,  $\times 475$

In the endeavor to estimate the degree of hypertrophy of the walls of the arterioles and the degree of obstruction produced by the hypertrophy of the media and proliferation of the intima, the most satisfactory method was to measure the thickness of the wall and the diameter of the lumen, and to estimate the ratio of the one to the other. Such measurements had been attempted by Gull and Sutton and by Ewald. However, as stated previously, their histologic specimens were not prepared according to the usual modern technic, the figures they obtained, therefore, cannot be compared with those of the present study. Since normal arterioles had never been measured in this manner, it was necessary to obtain a series of normal controls, therefore, fifty control cases

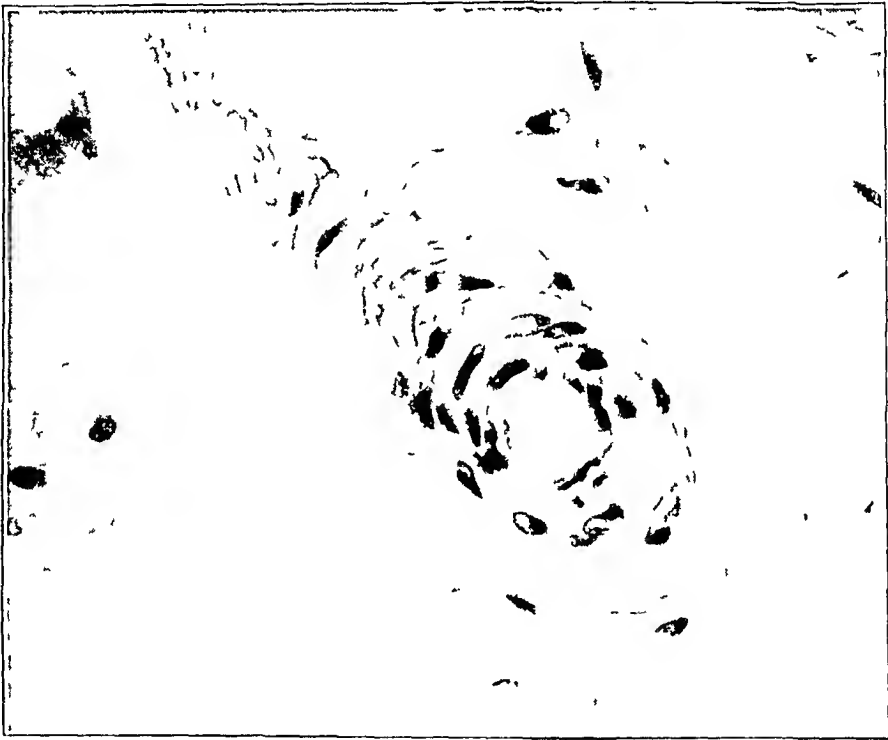


Fig 5 (case 48) —An arteriole from pectoralis major muscle obtained at biopsy. The thickness of the wall due to hypertrophy of the media and increase in number of nuclei in the musculature may be noted. Hematoxylin and eosin stain,  $\times 475$ .

were examined. The Bausch and Lomb micrometer was used and only vessels cut at right angles to their course were measured. Figure 8 shows diagrammatically the method of determining the ratio of wall to lumen. The distances *a-b*, *c-d*, *e-f*, and *g-h* were added and divided by four, giving the average for the vessel wall, the distances *b-c* and *f-g* were added and divided by two, giving the average for the lumen. Such estimations were made on several arterioles in each specimen of muscle and the average ratio was taken.

Such measurements of the arterioles show that in the normal one the average ratio of vessel wall to lumen is 1:2, with variations from



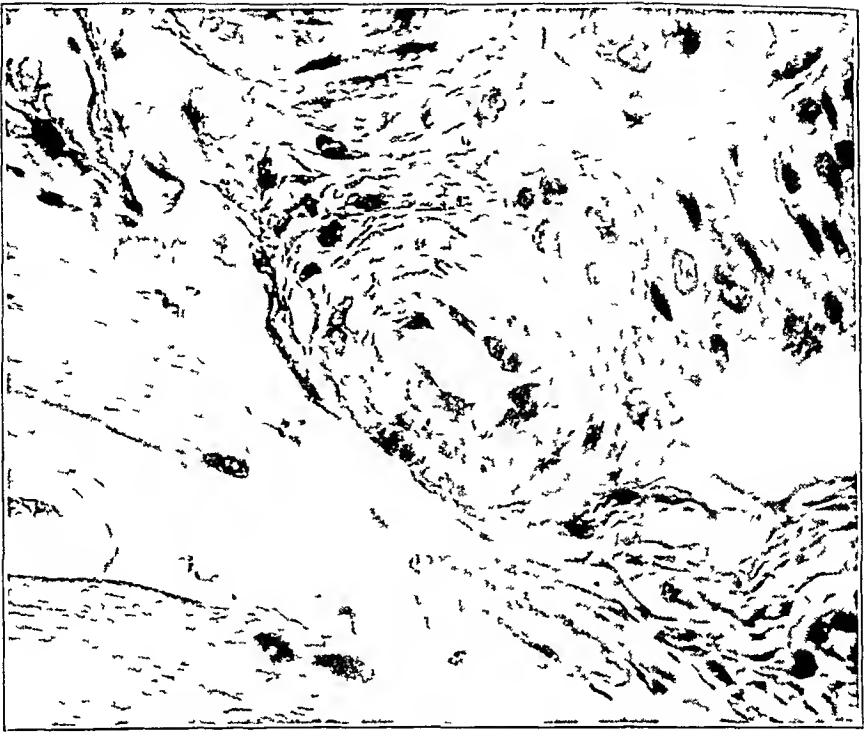
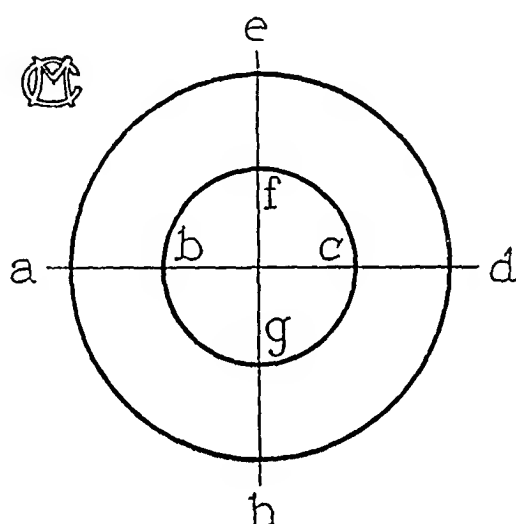


Fig 6 (case 40) —An arteriole from pectoralis major muscle obtained at biopsy showing thickening of muscle tissue in media, due to hypertrophy, with increase in number of nuclei. Hyperplasia of the endothelial cells in the intima may also be noted. The vessel wall is almost as thick as the lumen is wide. Van Gieson stain,  $\times 350$



Fig 7 (case 46) —An arteriole from pectoralis major muscle obtained at biopsy. There is increase in the number of nuclei of the media. There is definite thickening of the media, with hypertrophy. The normal 2:1 ratio of lumen to wall is upset. There is no fibrosis or necrosis in the media. Van Gieson stain,  $\times 350$

1.17 to 1.27<sup>30</sup> In our cases of benign hypertension, the average ratio was 1.14, with variations from 1.11 to 1.18, cases of severe benign or early malignant, and malignant hypertension show practically the same, an average ratio of wall to lumen of 1.11, with variations from 1.09 to 1.17. The figures indicate that, in spite of some overlapping, there is a definite difference between the average ratio obtained for arterioles in the normal states and the average ratio obtained for them in benign and malignant hypertension. It should be pointed out that it seems impossible with this measurement of the arterioles to distinguish the severe benign or early malignant group from that of malignant hypertension (table 1 and fig 9).



Cross section of small artery or arteriole

Fig 8—A method of determining the ratio of wall to lumen in arterioles

It is of interest, however, that in only five of the thirty-four cases with a wall-to-lumen ratio of 1.12 or less was the maximal diastolic pressure less than 140 mm.

*Necropsy*—In two cases of malignant hypertension (cases 40 and 46), necropsies were performed two and four months after the biopsies. A summary of the clinical data and of the gross and histologic changes follows (figs 10, 11, 12, 13, 14 and 15).

**CASE 40**—A man, aged 23, entered the hospital, Oct 29, 1927, he had suffered from a sudden paralysis eight days before. He had had frontal headaches and occasionally epistaxis from ten to twelve years previously. Hypertension had been discovered seven years before. Eight days before admission, he had been knocked

<sup>30</sup> In case 53, one of chronic glomerulonephritis, the ratio was normal, 1.18. Biopsy at the time of writing was being carried out in a series of such cases.

from the seat of a truck, and after driving the truck home, he had walked into the house, lain down and become irrational. Right hemiplegia had occurred. There had been some improvement after a few days.

General examination disclosed right hemiplegia. The blood pressure was 190 systolic and 145 diastolic. There was retinitis, grade 2, stage 2 to 3 of malignant hypertension type. The heart was enlarged (grade 1) as revealed by roentgen ray. There were inverted T waves in leads I and II of the electrocardiogram with a questionable coronary T wave in leads I and II. Examination of the urine gave negative results. The phenolsulphonphthalein test of renal function gave a return of dye of 50 per cent, and the blood urea was 40 mg for each hundred cubic centimeters. The Wassermann reaction of the blood was strongly positive, as was also the Kolmer modification of the Wassermann reaction of the spinal fluid.

The patient received one course of antisyphilitic treatment and returned home slightly improved. He continued treatment at home, the hemiplegia gradually

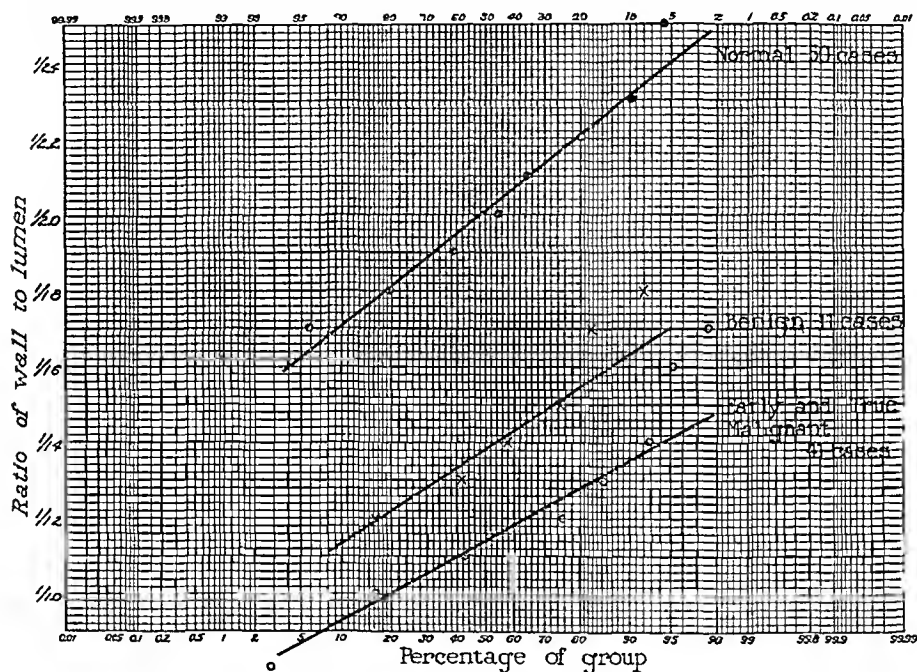


Fig 9—Three curves plotted on arithmetic probability paper. The ratios of the walls to the lumen of the arterioles are plotted as ordinates against the percentage number of cases as abscissas. The lower ratios may be noted particularly in the early and true malignant groups.

became less noticeable and he came back, April 23, 1928, for another course of treatment. At this time the blood pressure was 250 systolic and 175 diastolic, the heart was enlarged to grade 2, and there were signs of residual right hemiplegia. Blood urea was 54 mg for each hundred cubic centimeters. On April 27, 1928, the patient died from cerebral hemorrhage following convulsions. The urine obtained from the bladder at necropsy contained albumin, grade 4, and red blood cells.

The clinical diagnosis was malignant hypertension, cerebral hemorrhage and tertiary syphilis involving the central nervous system (vascular type).

Examination from the standpoint of gross pathologic anatomy revealed atrophy of the muscles of the right forearm and leg and a heart weighing 474 Gm (normal 300 Gm). There were moderately large subendothelial hemorrhages

in the left ventricle of the heart. The right coronary and noncoronary cusps of the aortic valve were bound together by firm fibrous adhesions for a distance of about 3 cm. The commissure was thickened and a fibrous band, 3 mm in diameter, extended up the aorta for a distance of 1 cm to a point at which it gradually blended into the intima of the aorta. In the remainder of the aorta there was arteriosclerosis, grade 1. The lungs, spleen, liver, gallbladder and bile ducts, stomach, pancreas, bladder, prostate, testes, trachea, thyroid gland, thymus and esophagus appeared normal. The kidneys weighed 145 and 188 Gm., respectively, but except for accentuated fetal lobulations, they appeared grossly normal. The brain externally appeared normal, but on section both lateral ventricles were dilated to grade 3, and were filled with partially clotted blood. There was a hemorrhage in the substance of the brain in the region of the right basal nuclei and an old infarct in the left lenticular nucleus.



Fig 10 (case 40)—An arteriole in pectoralis major muscle obtained at necropsy. Changes similar to those described in muscle obtained at biopsy (fig 6) may be noted. There is proliferation of endothelial cells of the intima, the number of nuclei in the media may be noted. Van Gieson stain,  $\times 350$ .

On histologic examination, the thyroid gland and the lungs were found to be essentially normal. In sections of the myocardium, liver, pancreas, suprarenal glands, prostate gland, testes and epididymis there were no changes except a slight but definite increase in the thickness of the walls of the arterioles. The trabeculae of the spleen were prominent and the walls of the arterioles were markedly thickened. There was irregular thickening of the walls of the arteries of medium size, suggesting organized mural thrombi.

Numerous sections of the kidneys showed them to be remarkably normal. There was partial or complete hyalinization of a few glomeruli, the remainder were normal. The tubules appeared normal. The walls of the arterioles were definitely but not markedly thickened (figs 11 and 12). In a section of the wall of the

ascending aorta were diffuse perivascular collections of lymphocytes around the vasa vasorum of the adventitia. Sections through the old infarct in the left lenticular nucleus showed degenerative changes in the nerve cells and diffuse glial proliferation. There was marked thickening of the walls of all the arterioles. Indefinite, patchy, acute degeneration with numerous areas of hemorrhage was found in the right basal ganglions, and the walls of the arterioles here and in the frontal lobe were only slightly thickened. There was no evidence of perivascular lymphocytic collections in any of the sections.

The anatomic diagnosis was malignant hypertension with cardiac hypertrophy, cerebral hemorrhage into the basal nuclei and ventricles, old infarct of the left lenticular nucleus, syphilis of the central nervous system (vascular type) syphilitic aortitis with cohesion of the aortic cusps and subendocardial hemorrhage of the left ventricle.



Fig 11 (case 40) —Cortex of kidney obtained at necropsy. Glomeruli and tubules appear normal. There is a small amount of fibrosis around the small arteries, which have definitely thickened walls. Hematoxylin and eosin stain,  $\times 75$ .

CASE 46 —A man, aged 33, came to the clinic in April, 1913, with a sacro-iliac strain. The systolic blood pressure at that time was 125. He returned three years later for appendectomy. On March 10, 1928, he came complaining of having had, for two and a half years, severe morning headaches, often associated with vomiting and nocturia. At the onset of the headaches, the systolic blood pressure was 160. For the six months previous to admission, he had had dyspnea on exertion, with a sense of constriction in the chest, and aching in the precordium. For two months, he had had a sharp epigastric pain after exertion.

On examination, the transverse diameter of the heart measured 14 cm, the aortic second sound was accentuated. There was peripheral sclerosis, grade 3.

The edge of the liver was palpable. The blood pressure was 210 systolic and 150 diastolic. There was albuminuria, grade 3, with hyaline and granular casts. The erythrocyte count was normal, hemoglobin was 73 per cent. The phenolsulphonphthalein test of renal function gave a return of dye of 30 per cent, and the blood urea was 60 mg in each hundred cubic centimeters. There were inverted T waves in leads I and II of the electrocardiogram. There was sclerosis of the retinal arteries, grade 3, and retinitis of the malignant hypertension type with edema of the disks of 2 diopters. Examination of capillaries at the nailfold revealed swift flow in moderately contracted, tortuous vessels.

The patient was sent home with directions to use a diet low in protein and in salt, but he returned, May 13, 1928, because of gastric distress, anorexia, nausea and vomiting. For three days, he had been orthopneic. There had been no edema.

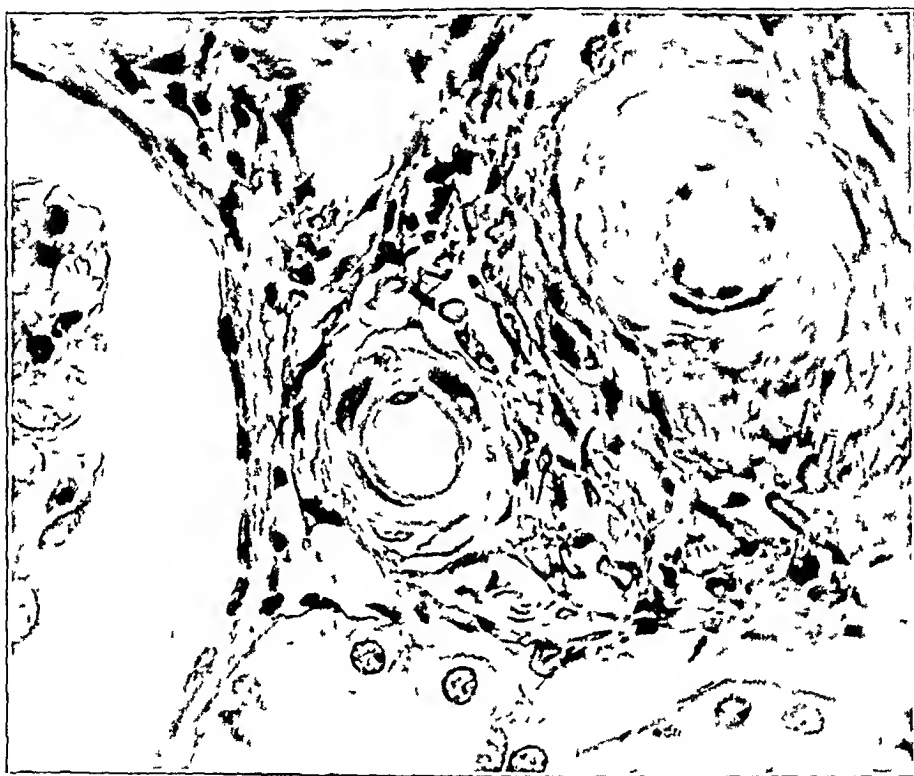


Fig 12 (case 40)—Arterioles from kidney obtained at necropsy. Thickening of the wall, especially of the tissue of the media, may be noted. One vessel shows areas of so-called necrosis. Van Gieson stain,  $\times 350$ .

and but slight hemoptysis. He had suffered also from some oliguria and blurring of vision.

On examination, the patient was orthopneic and his breath had an odor that suggested the presence of uremia. The heart was enlarged to grade 3. The blood pressure was 245 systolic and 150 diastolic. The fundus presented the same picture as before, but in addition there were generalized retinal edema, cotton wool exudates and hemorrhages. Hemoglobin was 40 per cent. There was albuminuria, grade 2. The blood urea was 274 mg, and creatinine 122 mg for each hundred cubic centimeters. The patient's condition progressively grew worse and he died nine days later. Signs of acute pericarditis, Cheyne-Stokes respiration and coma had developed. The blood urea in these last days rose to 561 mg, and the blood creatinine to 272 mg in each hundred cubic centimeters.

The clinical diagnosis was malignant hypertension, chronic myocardial degeneration (decompensated), acute pericarditis, general and renal sclerosis of the arteries and arterioles, and uremia

Examination for features of gross pathologic anatomy did not reveal edema, although the peritoneal cavity contained 50 cc of clear, straw-colored fluid. Both pleural cavities were practically obliterated by fibrous adhesions. The pericardial cavity contained 100 cc of cloudy, brown fluid, in which were flakes of fibrin. The heart weighed 618 Gm. On both visceral and parietal pericardial surfaces were roughened, hyperemic areas, covered with thin layers of soft exudate. There was sclerosis of the coronary arteries, grade 2. The left ventricle was dilated to grade 2. The valves and myocardium appeared normal. The aorta showed evidence of arteriosclerosis, grade 1. There was emphysema, grade 2, in the apexes of both lungs. In the right upper lobe near the hilum were two small caseating tubercles. The large bronchi of the right lung were hyperemic and were filled with mucopurulent material. In some places there were slight saccular dilatations. Bilaterally there was tuberculous caseation and calcification of the hilar lymph nodes. There was slight, old perisplenitis. The liver weighed 1,900 Gm and was chocolate-colored, and cut sections had a typical nutmeg appearance. The gall-bladder and biliary tracts, the stomach, pancreas, intestines and suprarenal glands appeared normal. The kidneys weighed, respectively, 125 and 118 Gm. Their surfaces were granular, mottled and pinkish-gray and had numerous punctate hemorrhages. The cut surface was pale, markings were obliterated and there were numerous punctate hemorrhages. There was definite, symmetrical atrophy of both cortex and medulla and the corticomedullary vessels were prominent and gaped. There was noticeable hypertrophy of the wall of the main renal artery. The median lobe of the prostate was slightly enlarged.

On histologic examination, sections of the prostate and thyroid glands were essentially normal. The walls of the arterioles of the pancreas, suprarenal glands, spleen and stomach were definitely thickened. There was, also, moderate congestion in the spleen. There was a small leiomyoma in the wall and a polyp of the stomach. There was some diffuse atrophy of the hepatic cells, which contained a fair amount of finely divided fat, particularly those in the central zones. The lungs were normal, except for active tuberculosis in the margins of one of the caseating tubercles. In the heart there was definite proliferation of the epicardial endothelium and there were scattered lymphocytes through the subepicardial fat. On the surface of the endothelium was a loosely adherent, amorphous acellular exudate. There was some variation in the size and shape of the nuclei of the muscle fibers and the fibers were more than normally spread apart by loose fibrous tissue. There was definite uniform thickening of the walls of the coronary arterioles. Sections stained for fat were negative. In the kidney, at least 60 per cent of the glomeruli appeared normal, except for some contraction and atrophy of the tufts. About 30 per cent were completely hyalinized. In the remainder were varying degrees of hyaline fibrosis, adhesions of tuft to capsule and, in one or two, weak attempts at capsular epithelial proliferation. In a few, the capsular spaces were filled with blood. There were extreme changes in the tubules, most of them were atrophied and constricted. Some were dilated and contained much hyaline material and debris. Many had been completely destroyed, and many contained considerable fat. There was a marked diffuse increase of rather acellular, fibrous interstitial tissue, with a few large areas of hemorrhage and a few small infarcts. The medium-sized and smaller arterioles were prominent and tortuous. In their walls was an extreme degree of thickening, proliferation and fibrosis, with marked splitting of the internal elastic laminae, and in many places the lumen was so constricted as to be barely visible (figs 14 and 15).

The anatomic diagnosis was malignant hypertension with sclerotic atrophy of the arterioles of the kidneys and cardiac hypertrophy, acute fibrinous pericarditis, dilatation, grade 2, of the left cardiac ventricle, benign prostatic hypertrophy, grade 1, healed and active tuberculosis of the pleura, lungs and hilar lymph nodes, and acute purulent bronchitis

Detailed histologic study and measurements of the peripheral arterioles in various tissues of these two cases revealed practically the same change both in the structure of the vessels and in the ratio of vessel wall to lumen, as observed in the previous biopsy (figs 6, 7, 10 and 13) The arterioles in the kidney (figs 12 and 15) were more extensively and seriously involved than vessels elsewhere Some of them were almost



Fig 13 (case 46)—An arteriole in pectoralis major muscle obtained at necropsy The changes are similar to those seen in the muscle obtained by biopsy Hematoxylin and eosin stain,  $\times 350$

completely occluded In case 40 (fig 11), the glomeruli were well preserved, and there was no glomerulonephritis, whereas in case 46 (fig 14) there were early fibrosis and atrophy of glomeruli, and many tubules had been destroyed This picture has been termed by Ellis<sup>31</sup> secondary ischemic nephritis Some of the small arteries and some arterioles showed evidence of the so-called necrosis of the media that has been described by Fahr<sup>12</sup> and others<sup>32</sup> (fig 15) It seems to us that this could be

31 Ellis, Arthur, quoted by Brain, R T, and Kay, H D A New Test of Renal Function, *Quart J Med* **22** 203, 1929

32 Herxheimer (footnote 10) Stern (footnote 11)



explained on the basis of ischemia rather than on that of the presence of a specific toxin. The blood supply to such vessels is supposed by many to come from the lumen and if, after marked hypertrophy with subsequent narrowing of the lumen, the blood supply is inadequate, ischemia, with fatty changes and necrosis, readily may follow.

#### COMMENT

The results of this study indicate that associated with hypertension a diffuse disturbance of the arterial side of the vascular system exists both clinically and histologically in varying degrees of severity.

In benign hypertension there may be no lesions in the peripheral arterioles or there may be moderate ones. Allbutt<sup>33</sup> considered dynamic

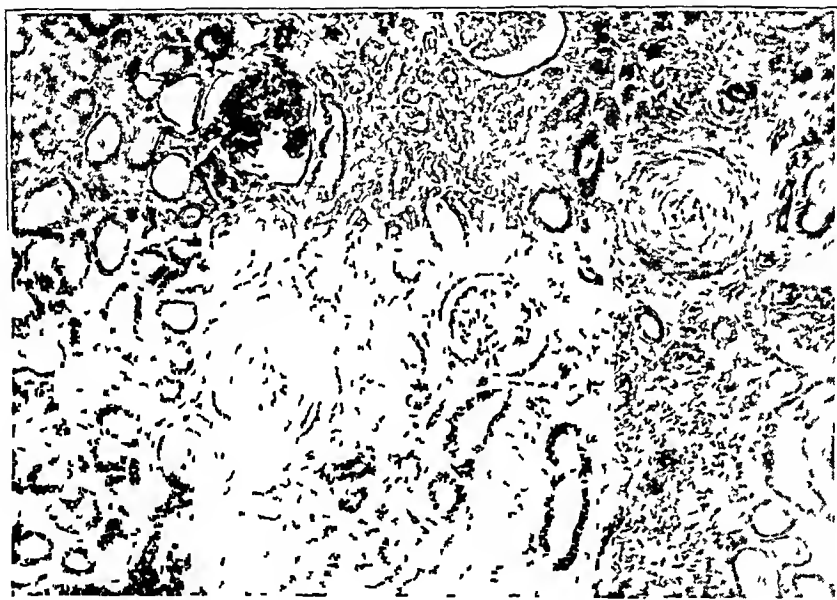


Fig 14 (case 46) —Cortex of kidney obtained at necropsy. Extreme thickening of arterioles may be seen and marked increase in the interstitial connective tissue. The glomeruli show early fibrosis and atrophy, and many tubules have been destroyed. Hematoxylin and eosin stain,  $\times 75$ .

narrowing, rather than organic changes in the arterioles, as the primary lesion. Our data, obtained at biopsy, are in harmony with the long retention of adequate retinal, cardiac and renal function and with the stationary or slow progression of the general condition. In the second group of cases, those of severe benign or early malignant hypertension, the clinical observations indicate more serious involvement. The blood pressure generally is higher, retinal and palpable peripheral arteriosclerosis is more marked, distinct, although often slight, abnormalities in the

<sup>33</sup> Allbutt, C. Senile Plethora or High Arterial Pressure in Elderly Persons, *Tr. Hunterian Soc.*, 1895-1896, p. 38.

electrocardiogram and the renal function are more frequently present. In spite of these clinical evidences of diffuse involvement, and a corresponding marked pathologic change in the peripheral arterioles that often is present, many of these patients still have remarkably good retinal, cardiac and renal function. Such results suggest that either the lesion in the arteriole, although marked, has been of shorter duration, or better compensation has taken place. In our cases of malignant hypertension there has been a definite type of retinitis. Cardiac enlargement and early disturbances of cardiac and renal function are more often present than in either of the other groups. The blood pressure usually is high, but

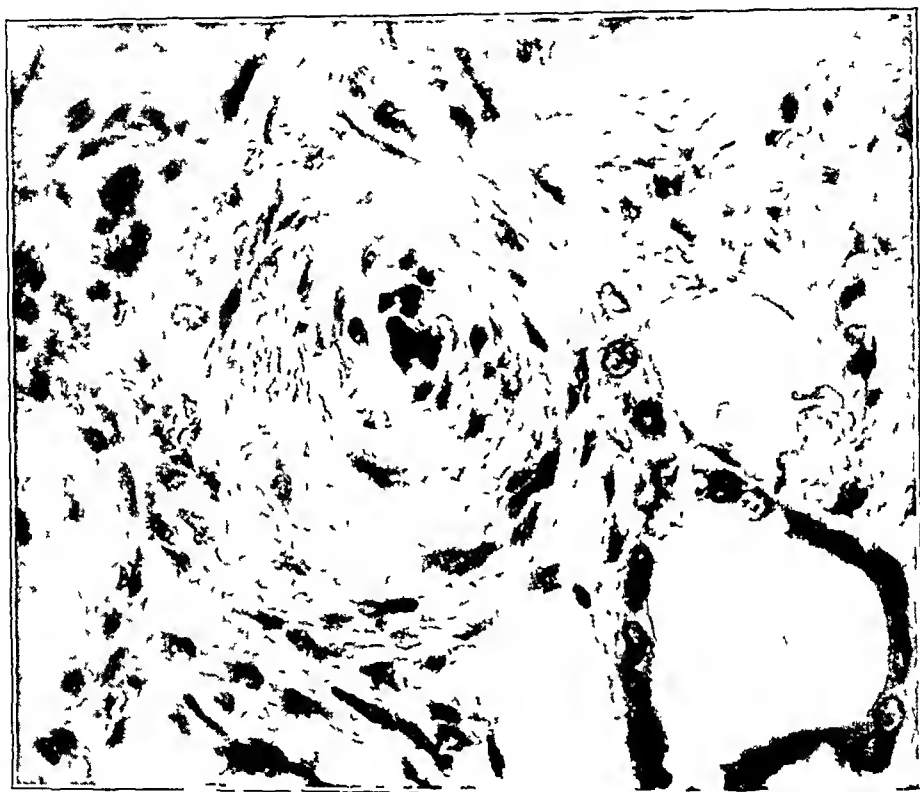


Fig 15 (case 46) —A small artery in the kidney, obtained at necropsy. The lumen is almost obliterated, and thickening of the wall is extreme. There is proliferation of endothelial cells of the intima. The number of cells in the musculature of the media and the area of necrosis which may be ischemic in origin may be noted. Hematoxylin and eosin stain,  $\times 350$ .

we have seen a few instances in which the blood pressure was only moderately increased, yet other features of the syndrome were present. There is almost invariably a marked thickening of the wall and narrowing of the lumen of the arteriole in muscles. The clinical course is rapidly progressive. In other words, there are good reasons for considering malignant hypertension as the terminal stage of the severe benign or early malignant type. We also have seen cases which undoubtedly belong to the benign group but which, at a later date, present the classic fea-

tures of the malignant type. Thus, there is clinical and pathologic evidence, in certain instances, at least, that the basic lesion in the three groups is one of degree. On the other hand, we recognize that in the great majority of cases of benign hypertension, the malignant syndrome never develops. In consideration of these facts, any possible theory as to the cause of diffuse vascular hypertensive disease must explain (1) the slow progression in benign hypertension, (2) the rapid development and course of malignant hypertension, particularly in the young, (3) the gradual transition from the clean-cut picture of benign to that of malignant hypertension, and (4) the occasional development of malignant hypertension in cases of chronic glomerulonephritis.

When a lesion was present in the arterioles of voluntary muscle, the chief pathologic changes were hypertrophy of the media, proliferation of the intima and marked reduction in the ratio of wall to lumen. There were no actual signs of degeneration or changes similar to those of senile retrogression. The facts that certain lesions were found in the arterioles of muscle obtained during life, and that later, at necropsy of the same patients, identical lesions were found and that similar lesions also were present in the arterioles of many organs afford significant evidence that the changes observed in arterioles of muscles are indicative of diffuse vascular disease. The lesion, if progressive, also offers a possible explanation of the widespread focal lesions seen at necropsy in cases of malignant hypertension. In our experience, the presence or absence of this lesion in the arterioles of muscles may determine the diagnosis and prognosis in the individual case. The frequent absence of any lesion in the arterioles of voluntary muscle obtained at necropsy in cases of essential hypertension, as reported by Jores,<sup>5</sup> Fahr,<sup>12</sup> Evans<sup>13</sup> and Fishberg,<sup>14</sup> seems best explained by the fact that their series, perhaps, did not include cases of the serious progressive type of hypertension, such as those which we have classed as cases of early malignant or malignant hypertension.

The type of lesion in the arteriole suggests hypertrophy in the face of excessive strain. One interpretation would be that the lesion is secondary to the hypertension. However, there are cases of malignant hypertension in which there is only a moderate rise in blood pressure, this might indicate that the diffuse involvement of the arterioles is primary, and that sustained hypertension might result on account of increased peripheral resistance. More facts are needed to explain the mechanism of the intricate balance between the output of the heart and the changes in the peripheral vascular structures.

The ophthalmoscopic observations of Wagener<sup>34</sup> in certain cases of this series are of great interest. He noted occasionally in the absence of

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34 Wagener, H. P. Personal communication to the author.

definite sclerosis a marked narrowing of the small retinal arteries, which was due to actual vasoconstriction, later these same arteries showed evident sclerosis of their walls. This observation suggests that marked, continuous vasoconstriction may precede and later may give rise to demonstrable histologic change in the arterioles. The uniform occurrence of hypertrophy in the circular muscular layer of the arteriole lends support to such a theory of development.

Certain physiologic and clinical observations on the capillaries have a possible bearing on this point. Richards and Schmidt,<sup>35</sup> from direct observation of the vessels of the kidney of the frog, observed that the slitlike opening at the juncture of the afferent glomerular arterioles and the glomerular capillaries is especially susceptible to constrictor influence. These authors also observed a similar phenomenon in the arterioles in the muscle of the frog. Landis,<sup>27</sup> in his micropressure determinations in the mesentery of the frog, noted a sharp reduction in pulse pressure at the arteriole-capillary juncture, and suggested that this fall may be partly due to similar narrow openings at the points where the capillaries spring from arterioles. Brown and Roth<sup>36</sup> suggested that the fast, spurting or jerky flow seen in the capillaries at the nailfold in many cases of hypertension may be due to a possible disturbance of the precapillary arterioles, an intermittent closure of the vessels. They believed that this periodic closure may be a factor in the production of increased peripheral resistance.

The primary cause of diffuse hypertensive vascular disease is still mysterious. Syphilis is so rarely present that it does not seem to be a factor. It is difficult to accept the conclusion of Fahr that the hypertension in all cases is of renal origin. Two general possibilities seem more probable. Hypertension, it seems, may be due to an inherent disturbance of the sympathetic nervous system or it may be due to the action of a hypothetic pressor substance on the sympathetic chain, on sympathetic endings in the wall of the arteriole or directly on the smooth muscle of the vessel wall.

#### SUMMARY

The arterioles in voluntary muscle of ambulatory patients with diffuse hypertensive vascular disease frequently show distinctive histologic changes. These changes differ in degree and may afford a valuable index for predicting the ultimate outcome in the individual case.

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35 Richards, A. N., and Schmidt, C. F. A Description of the Glomerular Circulation in the Frog's Kidney and Observations Concerning the Action of Adrenalin and Various Other Substances upon It, *Am J Physiol* **71** 178, 1924-1925.

36 Brown, G. E., and Roth, G. M. Biomicroscopy of the Surface Capillaries in Normal and Pathologic Subjects, *M J Australia* **1** 499, 1927.

# PROLONGATION OF THE LIFE OF NEPHRECTOMIZED DOGS

WITH THE PRODUCTION OF EDEMA \*

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AND

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WITH THE ASSISTANCE OF F S BARRY

CHICAGO

The object of this research was to determine by what means life could be prolonged most effectively following double nephrectomy and to study the effect of these methods on the blood chemistry and resulting symptoms

Vicarious elimination has been suggested as the means by which substances usually eliminated by the kidneys may be secreted or excreted by the stomach, intestines, saliva, sweat and lungs <sup>1</sup>

Working on the theory that stimulation of those processes and organs which carry on vicarious elimination would result in a decreased retention of nitrogenous waste products and would prevent the absorption of toxic products from the intestines and thus prolong life, we studied the effects on nephrectomized dogs of procedures designed to increase the secretory and excretory activity of the gastro-intestinal tract

## LITERATURE

Brown-Sequard, in 1889, published his theory on internal secretions, in which the kidney was included as one of the organs of internal secretion, ascribing uremia to the failure or lack of such a secretion. In 1893,<sup>2</sup> he stated that while nephrectomized animals lived only thirty hours on the average, similar animals to which kidney extracts were given lived sixty hours. He concluded that the accumulation of the nitrogenous waste products was not the only factor responsible for the appearance of uremic symptoms, the disturbance of the internal secretion of the kidney being a more powerful and active factor

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1 McEnery, E T, Meyer, Jacob, and Ivy, A C J Lab & Clin Med  
12 368, 1927

2 Brown-Sequard Arch d phys norm et path 5 778, 1893

Herter and Wakeman<sup>3</sup> reported a study of the alterations in the composition of the blood resulting from double nephrectomy. They used dogs in most instances and removed both kidneys at one operation. They noted that these dogs developed a loss of appetite, drowsiness, vomiting, diarrhea and lowering of temperature. In a few instances, the second kidney was removed several days after the removal of the first. In a few others both ureters were ligated and the kidneys not removed. All the animals were bled about the time of impending death. Their investigations revealed that the alkalinity of the blood was increased, that the blood urea was increased to ten times the normal value in eighty-two hours or less, that the uric acid content of the blood was not increased, and that the alcoholic and ethereal extractives were increased. Eighteen dogs lived from twenty-two to eighty-two hours following double nephrectomy, the average being forty-eight hours. Six dogs lived from thirty-six to seventy-two hours following ligation of both ureters, the average being fifty hours. The blood urea in the nephrectomized animals varied from 103 to 458 mg per hundred cubic centimeters, the average being 315 mg. The tissues contained from four to five times more than the normal percentage of nitrogen, probably urea. This early work is open to criticism because of the great inaccuracy of the analytic methods employed.

Bradford,<sup>4</sup> in 1899, in a study of the kidney and metabolism, made a few observations on the results of double nephrectomy and ligation of both ureters. Of four animals in which both ureters had been ligated, two were bled to death seventy-two hours after the operation, and two were found dead on the morning of the third day, so that they lived between forty-eight and sixty hours. A double nephrectomy was performed in only one animal and this animal was bled to death seventy-two hours after the operation.

Vitzou,<sup>5</sup> in 1902, investigating the internal secretion of the kidney, claimed to have kept animals alive following a two-stage double nephrectomy for as high as from 146 to 164 hours by no other measure than injection of blood serum from renal veins of healthy animals of the same species. This he interpreted as due to the internal secretion of the kidneys.

Amos,<sup>6</sup> in 1905, pointed out a definite variability in the tolerance of different species of animals to renal intoxication. He found that guinea-pigs, after unilateral ureteral obstruction, lived for an average of nineteen and one-half days, whereas rats, under the same conditions,

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3 Herter and Wakeman. *J Exper Med* **4** 117, 1899.

4 Bradford, J. R. *J Physiol* **23** 415, 1899.

5 Vitzou, A. N. Bucharest, 1902.

6 Amos, B. *J Path & Bact* **10** 265, 1905.

lived for an average of fifty-two days, but in each species, when both ureters were simultaneously ligated, the animal died in two days

In the experiments of Ajello and Parascandalo, as quoted by Pearce,<sup>7</sup> twelve control dogs died in from four to forty-eight hours after double nephrectomy with symptoms of dyspnea, convulsions and gastro-intestinal disturbances considered to be uremic, while of ten nephrectomized dogs treated with glycerin extracts of kidney substance, one lived four days, six lived three days, and three died in from forty-eight to fifty-two hours. Many other investigations give similar results

While studying the effects of reduction of the kidney substance, Kaisner, Bunker and Grabfield<sup>8</sup> noted that following the removal of the total kidney substance the urea nitrogen content of the blood increased until death intervened. The average length of life following total nephrectomy in three dogs was seventy-six hours, one dog lived ninety-six hours. The average urea nitrogen content of the blood was 285 mg per hundred cubic centimeters

In 1921, Foster<sup>9</sup> noted that in nephrectomized dogs the urea formed 60 per cent or more of the total nonprotein nitrogen, while in uremia it seldom formed more than 65 per cent and often less than 50 per cent of the total nonprotein nitrogen

Wallace and Pellini<sup>10</sup> observed that double nephrectomy failed to produce acidosis. They made their observations on two dogs, both of which lived four days following the operation

Allen, Scharf and Lunden,<sup>11</sup> in a report of a study of experimental nephritis, stated "Total nephrectomy produces a condition which in dogs is acutely fatal, generally within a couple of days. Nitrogen retention and acidosis are demonstrable, but death occurs from weakness without edema, hypertension or any of the clinical phenomena of nephritis. The same procedure when carried out in goats yielded better results, these animals surviving total nephrectomy for two weeks." They could not produce edema even in partially nephrectomized dogs with the heaviest feeding of salt

Putaszek<sup>12</sup> recently reported that he was unable to obtain very marked symptoms of acid intoxication in dogs surviving from two to

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7 Pearce, R. M. The Theory of Chemical Correlation as Applied to the Pathology of the Kidney, *Arch Int Med* **2** 77 (Aug) 1908

8 Karsner, Bunker, and Grabfield. *J Exper Med* **22** 544, 1915

9 Foster, N. B. *Uremia*, *J A M A* **76** 28 (Jan 29) 1921

10 Wallace, G. B., and Pellini, E. J. *Capillary Poisons and Acidosis*, *Arch Int Med* **28** 711 (Dec) 1921

11 Allen, F. M., Scharf, F., and Lunden, H. *Clinical and Experimental Renal Deficiency*, *J A M A* **85** 1698 (Nov 28) 1925

12 Putaszek, L. *Compt Rend Soc de biol* **96** 567, 1927

five days after double nephrectomy. There was a small diminution in alkali reserve, but the slight decrease was in marked contrast to the fall observed in cases of human uremia. He expressed the opinion that when the kidneys are extirpated, some extrarenal mechanism maintains the alkali reserve approximately normal, whereas in uremia, the extrarenal mechanism breaks down along with the kidneys.

Andrews<sup>13</sup> reported several cases of dogs surviving from four to ten days following total nephrectomy. The animals did not show evidences of acid intoxication even in the terminal stages. They were active, played about and had good appetites. He injected hypertonic salt solution in such amounts that the chloride content of the blood was comparable to that in uremia, and reproduced every manifestation of uremia seen in the human being. Both the chloride and the water rapidly made their way from the blood into the tissues, the brain and liver showed the highest chloride content and were the organs chiefly involved. He assumed that degenerative changes in the liver due to an increased sodium-calcium content are the fundamental sources of the uremic toxins.

Swingle<sup>14</sup> recently reported a study of the acid-base equilibrium after bilateral nephrectomy. He employed a two-stage operation and reported eight dogs with an average postoperative life of eighty-five hours, the longest being 120 and the shortest sixty-six hours. He stated that although a slight fall in alkali reserve may occur, the animals do not develop acid intoxication. He found retention of sulphate, phosphate and urea, and a diminution of blood chlorides. He felt that the decrease in chlorides which occurred was not due to chlorides lost in the vomitus, because one of the dogs did not vomit.

From these investigations it is seen that the length of life following total nephrectomy is extremely variable. The average length of life in these animals is about seventy-two hours. The extremely low figures on survival time, of from four to twenty-four hours, must have been due to operative procedure. The earlier investigations of the alterations of the composition of the blood resulting from double nephrectomy are open to criticism because of the methods of analysis employed at that time.

#### EXPERIMENTAL METHODS

Large, well nourished dogs, averaging in weight about 18 Kg, were employed as experimental animals. These animals were specially selected, being in the best physical condition, the smaller dogs were rejected because it was our experience, as well as that of others, that the larger and more vigorous animals survive bilateral nephrectomy longer than the smaller dogs. They were kept in the laboratory several days before using in order to accustom them to their new sur-

13 Andrews, E. Experimental Uremia, Arch Int Med **40** 548 (Oct) 1927

14 Swingle, W. W. Am J Physiol **86** 450, 1928



roundings and to obtain the normal blood chemistry values. In all cases, except groups II and IX, the animals were fed raw ground meat mixed with bread.

The animals in groups II and IX were fed 200 Gm of bread, 500 cc of milk, and from 100 to 150 Gm of lactose each day before operation until they developed diarrhea. After operation this diet was continued by forced feeding when necessary in group II. But the animals in group IX were allowed to go without food when they refused it. Specimens of blood were drawn from the saphenous vein by the use of a syringe.

Both kidneys were removed in one operation. Through a midline incision, after severing of the peritoneal fold at the upper pole of the kidney, the kidney was delivered and decapsulated. The renal vessels were clamped, doubly ligated and cut. The ureter was ligated separately and cut. All dogs were given a pre-operative injection of  $\frac{1}{2}$  gram (832 mg) of morphine sulphate and  $\frac{1}{100}$  gram (0.6 mg) of atrophine sulphate. Anesthesia was induced with ether. The period of operation was from fifteen minutes to one-half hour.

The analysis of the blood was performed according to the method of Folin and Wu. A protein-free filtrate was prepared and examined for nonprotein nitrogen, urea nitrogen, creatinine and chlorides.

Group I. The dogs in this group were fed a meat diet, and were used as controls.

Group II. These dogs were put on the lactose diet described, for from seven to ten days before operation, and after operation were fed by tube when they refused to eat.

Group III. Following bilateral nephrectomy the animals in this group fed a meat diet, were given injections of 2 mg of histamine subcutaneously, two to three times a day.

Group IV. These animals, also fed a meat diet, were given from 1 to 2 ounces of magnesium sulphate before operation until diarrhea occurred, and following operation, by tube when necessary.

Group V. Following operation, these animals, fed a meat diet, were given a daily intravenous injection of Ringer's solution with increased sodium bicarbonate content. This solution, which we called "sodium bicarbonate Ringer's," was made up as follows: sodium chloride, 0.45 per cent, potassium chloride, 0.42 per cent, calcium chloride, 0.24 per cent, and sodium bicarbonate, 0.65 per cent.

Group VI. The same diet was used in this group. Following operation, the animals were given a daily intravenous injection of Ringer's solution made as follows: sodium chloride, 0.9 per cent, potassium chloride, 0.42 per cent, calcium chloride, 0.24 per cent, and sodium bicarbonate, 0.02 per cent.

Group VII. These animals, fed a meat diet, were given from 1,000 to 1,500 cc of Ringer's solution subcutaneously, each day, in two or three doses.

Group VIII. A meat diet was used in this group and from 1,000 to 1,500 cc of bicarbonate Ringer's solution given subcutaneously, each day following operation.

Group IX. Lactose diet was instituted preceding the operation until diarrhea developed. After the operation, from 1,000 to 1,500 cc of Ringer's solution was given subcutaneously each day.

## RESULTS

*Group I* (tables 1 and 2).—There were six animals in this group, and their average weight was 17.7 Kg. They were kept on a meat diet before operation and for as long after operation as they would eat. In general, they appeared normal for about forty-eight to sixty hours after operation and occasionally for three days. They ate, walked about and

seemed in excellent condition. The first symptoms were "malaise" and loss of appetite. They sniffed at offered food, possibly ate a bite or two and then turned away. Then they became listless, lying quietly for hours at a time, but when aroused, walked about in normal fashion. In this group, vomiting appeared as a rule on the third day, the vomitus consisting of bile stained fluid and mucus. Diarrhea soon set in and in some cases, especially as the end approached, the stools became bloody. As symptoms progressed, the animals showed increased weakness, especially of the hind legs, and swayed from side to side when walking. As the terminal stage approached, the animals passed into increasing stupor, then into coma, and finally died. One of the animals in this group showed marked salivation on the third day. The average length of life following bilateral nephrectomy in this group was 105.6 hours.

Analysis of the blood in these dogs showed a steady, day to day increase in the content of nonprotein nitrogen, urea nitrogen, creatinine, and a reduction of the chlorides. Normally, the ratio of the nonprotein nitrogen to urea nitrogen is usually 2:1, but as these substances accumulate following total nephrectomy the urea nitrogen increases at a greater rate than the nonprotein nitrogen, the ratio becoming 3:2.

Atchley and Benedict<sup>15</sup> observed diminution of the chlorides following bilateral ureteral ligation of dogs. They studied the chlorides lost in the vomitus and excreted in the feces, but they were unable to account for the loss on the basis of vomiting or excessive excretion. Study of chloride concentration of various tissues such as muscle and brain likewise failed to show deviations from the normal. They were unable to account for the fall in blood chlorides on the basis of their examinations.

The results of the daily examination of the blood of one of the dogs in this group are given in table 1.

Table 2 shows the duration of life, analysis of the blood just before death and time of appearance of vomiting and diarrhea of the animals in this group. At autopsy, the chief changes were found in the gastrointestinal tract and liver. The stomach presented a moderate degree of gastritis, and the lower portion of the ileum and colon were moderately inflamed. The liver was dark and congested. The brain was more wet and the cerebral vessels were more congested than normal.

*Group II* (tables 3 and 4) —There were eleven dogs in this group, and their average weight was 18.7 Kg. They were kept on a low protein lactose diet as described, and when diarrhea had been instituted, bilateral nephrectomy was performed. The average length of life following the operation in this group was 137.6 hours, an average of thirty-two hours longer than the controls. One animal in this group lived 194 hours, which was fifty-four hours longer than any animal in the control group,

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15 Atchley, D. W., and Benedict, E. M. *J. Biol. Chem.* **73**: 1, 1927.

and eighty-eight hours longer than the average for this group. In spite of the great variability in the length of life following total nephrectomy, both in these experiments and in those of other investigators, a comparison of the average length of life of the two groups may be made, because we feel that the groups include a sufficient number of animals.

After removal of both kidneys, the symptoms of latent uremia appeared as in the control animals, but were somewhat delayed.

The analysis of the blood of these dogs showed that the retention of the nitrogenous waste products does not occur as rapidly as in the control animals.

TABLE 1—*Typical Blood Observations on Control Dog 4, Group I, Following Nephrectomy*

Date	Hours After Operation	Weight, Kg	Nonprotein Nitrogen, Mg per 100 Cc	Urea Nitrogen, Mg per 100 Cc	Creatinine, Mg per 100 Cc	Chlorides as NaCl, Mg per 100 Cc	Comment
4/30/26		15.2	29.1	21.6	1.1	0.450	
5/ 1/26		15.2	29.6	22.4	1.4	0.445	Operation, 12 noon
5/ 2/26	22	14.8	72.2	33.4	3.43	0.431	
5/ 3/26	51	14.7	153.8	100.8	8.5	0.429	Vomited
5/ 4/26	70	14.6	201.6	182.0	10.1	0.387	Anorexia
5/ 5/26	93	11.3	238.0	235.2	12.5	0.412	Drowsy, vomited
5/ 6/26	122	12.8	403.2	257.2	14.7	0.341	Has diarrhea, vomited
5/ 6/26							Died in coma at 2 p m

TABLE 2—*Data on Control Dogs in Group I Following Nephrectomy*

Dog	Duration of Life, Hours	Nonprotein Nitrogen, Mg per 100 Cc	Urea Nitrogen, Mg per 100 Cc	Creatinine, Mg per 100 Cc	Chlorides as NaCl, Gm per 100 Cc	Vomiting, Hours	Diarrhea, Hours	Salivation, Hours
1	140	196.0	126.0	14.8	0.231	73	45	73
2	139	366.8		15.0	0.212	98	98	
3	88	196.0	100.0	10.5	0.396		72	
4	122	403.2	257.2	14.7	0.311	51	122	
20	60	251.4	127.6	12.1			41	
21	85	485.0	241.0	15.7			72	
Average	105.6	308.2	202.4	13.8	0.290	74	75	

Note: No edema nor convulsions were observed.

At autopsy, there was usually a more marked inflammation of the stomach and intestinal mucosa than occurred in the control animals, probably because of the longer life. The other changes were essentially the same. The results of the daily examinations of the blood of one of the dogs in this group are given in table 3, while table 4 includes the summary of the results obtained in the series.

*Group III* (tables 5 and 6).—There were seven animals in this group. Following bilateral nephrectomy, these animals received injections of histamine three times a day.

McEnery, Meyer and Ivy<sup>1</sup> have shown that in experimental nephritis the gastric glands respond to an injection of histamine and that urea is eliminated in the gastric secretions. We used this means of increasing vicarious elimination in this group of animals. And although we were

not successful in prolonging the life of these animals, the average length of life being ninety-eight and seven-tenths hours, the analysis of the blood revealed a definite delay in the retention of the nitrogenous waste products, and following the injections a drop was demonstrated in the content of nonprotein nitrogen, urea nitrogen and creatinine. In dog 47, the analysis of the blood at the fifty-third and the seventy-second hours showed only a slight rise in the creatinine and no increase in the content of nonprotein nitrogen and urea nitrogen over this period of nineteen hours. Another interesting observation in this group was the

TABLE 3—*Typical Blood Changes in Dog 9, Group II, Following Nephrectomy*

Date	Hours After Operation	Weight, Kg	Nonprotein Nitrogen, Mg per 100 Cc	Urea Nitrogen, Mg per 100 Cc	Creatinine, Mg per 100 Cc	Chlorides as NaCl, Mg per 100 Cc	Comment
7/26/26		19.5	25.2	14.0	1.5	0.41	Has diarrhea
7/27/26		19.5	32.8	13.0	1.5	0.41	Operation at 5 p. m.
7/28/26	14	18.4	56.0	37.2	3.19	0.39	Drank water
7/29/26	48	18.1	87.6	44.8	6.3	0.38	Fed by tube
7/30/26	64	18.1	120.4	104.0	9.0	0.38	
7/31/26	88	17.6	131.6	117.6	9.1	0.37	
8/ 1/26	112	17.2	163.8	124.5	10.5	0.37	
8/ 2/26	139	16.2	204.4	131.6	11.7	0.35	
8/ 3/26	167	15.9	151.2	105.0	13.0	0.35	
8/ 4/26	186	15.2	261.3	143.6	15.8	0.34	Vomiting, stupor, died in coma at 11 a. m.

TABLE 4—*Data on Dogs in Group II Following Nephrectomy*

Dog	Duration of Life, Hours	Nonprotein Nitrogen, Mg per 100 Cc	Urea Nitrogen, Mg per 100 Cc	Creatinine, Mg per 100 Cc	Chlorides as NaCl, Mg per 100 Cc	Vomiting, Hours
5	168	236.0	168.2	16.3	0.432	70
7	136	270.0	191.8	11.5	0.200	146
8	194	431.2	408.8	19.8	0.300	
9	186	261.3	143.6	15.8		
23	130	360.5	174.5	12.0		23
24	130	306.1	182.5	8.6		44
27	138	208.0	130.4	13.0	0.456	74
33	108	102.5	133.0	11.4	0.312	94
34	145	454.1	386.0	15.3	0.291	115
22	89	254.0	61.5	9.4		25
32	90	240.0	194.0	9.8	0.406	71
Average	137.6	283.8	189.2	12.08	0.217	73

development of convulsions in five of the seven animals. These began with slight muscular twitchings from two to ten hours before death, which increased in severity until definite clonic convulsions of all muscles were noted before death. Three of the animals in this group showed spasmodic contraction of the diaphragm synchronous with the heart beat.

The injection of histamine even in larger doses does not produce such results in normal animals.

The changes found at autopsy in these animals were similar to those observed in the control animals, except that in this group rigor mortis occurred soon after death.

Table 5 shows the results of an hourly analysis of the blood in one of three animals. Table 6 includes each animal in this series.

*Group IV* (table 7) —In this series there were six animals. They were given 1 or 2 ounces of magnesium sulphate by stomach tube every day before operation until diarrhea developed, and after operation until death. The average length of life in this group was eighty-nine hours.

TABLE 5—Data on Dog 47, Group III, Following Nephrectomy

Date	Hours After Operation	Nonprotein Nitrogen, Mg per 100 Cc	Urea Nitrogen, Mg per 100 Cc	Creatinine, Mg per 100 Cc	Comment
2/13/28	0	26.4	14.1	1.70	Meat diet, operation at 1 p. m.
2/16/28	47	122.0	72.0	7.23	Condition fine, ate and drank
	47				2 mg. histamine
	48	135.5	98.0	7.89	
	48				2 mg. histamine
	49.5	178.5	91.0	9.09	
	53	150.0	112.0	8.57	
2/17/28	72	150.0	112.0	9.6	Condition good
	72				2 mg. histamine
	73	146.5	95.2	10.2	
	73				2 mg. histamine
	74	189.0	88.0	11.1	
	78	186.0	112.0	10.6	
	81				2 mg. histamine
2/18/28					Spasmodic contraction of diaphragm
2/19/28	117	272.5	217.0	14.6	Condition poor
	117				2 mg. histamine
	118	275.0	196.0	15.3	
	118				2 mg. histamine
	119	267.0	200.0	15.7	
	123	309.0	238.0	15.7	

TABLE 6—Data on Dogs in Group III Following Nephrectomy

Dog	Duration of Life, Hours	Non protein Nitrogen, Mg per 100 Cc	Urea Nitrogen, Mg per 100 Cc	Creatinine, Mg per 100 Cc	Chlorides as NaCl, Gm per 100 Cc	Vomiting, Hours	Diarrhea	Salivation	Edema	Convulsions, Hours
36	118	292.5	244.5	17.1	0.270	115	0	0	0	115
46	104	236.0	210.0	10.2		69	0	0	0	102
47	130	309.0	238.0	15.7		97	0	0	0	?
48	82	175.0	98.0	9.2 at 48 hours		48	0	0	0	72
49	58					45	0	0	0	24
38	102					0	0	0	0	102
39	97					0	0	0	0	0
Average	98.7	253.1	197.6	13.0	0.27	74	0	0	0	5

*Groups V and VI* (tables 8 and 9) —There were two animals in each group. They received intravenously from 100 to 500 cc. of bicarbonate Ringer's or Ringer's solution intravenously at a single injection every day after operation. The average duration of life for those receiving bicarbonate Ringer's was ninety-four hours, and for those receiving Ringer's solution the average duration of life after operation was sixty-five hours. Dog 53 in group V showed a small amount of fluid in the pleural and peritoneal cavities at autopsy, none of the other animals developed edema or ascites. More animals were not used.

because of the deleterious action of the procedure (The solution was injected slowly, 20 cc per minute)

*Groups VII and VIII* (tables 10, 11 and 12) —Group VII includes nine animals which received Ringer's solution subcutaneously (from 1,000 to 1,500 cc daily in either two or three injections) with an average postoperative life of 165 hours, which is an average of sixty hours longer than the control animals. One of the animals (dog 57) lived 224 hours, which is 119 hours longer than the average life of a

TABLE 7—Data on Dogs in Group IV Following Nephrectomy

Dog	Duration of Life, Hours	Vomiting, Hours	Diarrhea	Edema	Convulsions
40	92	48	Instituted before operation	0	0
41	88	42	Instituted before operation	0	0
42	130	48	Instituted before operation	0	0
43	60	18	Instituted before operation	0	0
44	88	48	Instituted before operation	0	0
45	89	73	Instituted before operation	0	0
	89	46	Instituted before operation	0	0

TABLE 8—Data on Dogs in Group V Following Nephrectomy

Dog	Duration of Life, Hours	Vomiting	Diarrhea	Edema	Ascites	Convulsion	Bicarbonate Ringer's Injected Daily, Cc
50	84	0	0	0	0	0	500
53	104	48	0	0	0	95	100
Average	94						

TABLE 9—Data on Dogs in Group VI Following Nephrectomy

Dog	Duration of Life, Hours	Vomiting	Diarrhea	Edema	Ascites	Convulsions	Ringer's Solution Injected Daily, Cc	
51	69	48	0	0	0	0	500	
54	62	0	0	0	0	0	500	Pulmonary edema, jaundice
Average	65							

control animal and eighty-four hours longer than the best control animal. Two of these animals showed salivation, six of the nine had edema demonstrably before death, and six of them had collections of fluid in the pleural and peritoneal cavities demonstrable at autopsy. In dogs 57 and 61, ascitic fluid was removed by paracentesis twenty-four hours before death. At autopsy a marked cerebral and pulmonary edema was demonstrated in nearly every case. The analysis of the blood in this group demonstrated that instead of the usual drop in chlorides, there was a slight rise.

*Group VIII* —This group includes five animals which received bicarbonate Ringer's subcutaneously (from 1,000 to 1,500 cc daily in two or three injections) with an average postoperative life of 162 hours. Three of the five developed edema and four of them developed ascites.

*Group IX* (table 13) —There were five animals in this group, and they were given a preoperative diet of lactose, bread and milk until diarrhea developed. After operation they were given Ringer's solution subcutaneously, two to three times a day.

The average postoperative life of this group was 140 hours. Dog 18 lived 198 hours, which is ninety-three hours longer than the average.



Dog 57 which lived two hundred and twenty-four hours following double nephrectomy. This dog received 1,000 cc of Ringer's solution subcutaneously daily. Note the edema of the face, neck, limbs, body and the abdominal distention. Ascitic fluid was removed from this animal several times.

for control animals. Two of these animals salivated. The entire group developed edema and ascites.

#### COMMENT

There are several probable explanations which will account for the longer average postoperative life of the control animals than that observed by previous investigators. In the first place, the animals used in these experiments were all in the best physical condition and of an average weight of 18 Kg. When care is not employed in the selection of the animals and small animals in poor condition are used, the duration of life following total nephrectomy is much shorter. In the second place, the operative procedure used in these experiments was simple and rapid, thus reducing the postoperative shock to a minimum.

*Lactose*—The animals that were kept on a diet of lactose, bread and milk lived thirty-two hours longer than the control animals following double nephrectomy, and the nonprotein nitrogen, urea nitrogen and creatinine accumulated more slowly in these animals on a lactose diet

This can be explained by the fact that these animals were on a low protein diet, that the nitrogenous constituents of the blood were lower

TABLE 10—*Typical Blood Changes in Dog 1, Group VII, Following Nephrectomy*

Date	Hours After Operation	Weight, Kg	Nonprotein Nitrogen, Mg per 100 Cc	Creatinine, Mg per 100 Cc	Chlorides as NaCl, Gm per 100 Cc	Ringer's Solution Injected Daily, Cc	Comment
7/11/28		22.5	34.2	1.47			Operation at 6 p m
7/12/28	24	22.6	83.9	4.2		1,500	Condition good
7/13/28	48	23.6	230.5	8.0	0.447	1,500	Vomited, slight edema and salivation
7/14/28	72	24.0	300.0	8.7	0.468	1,500	Diarrhea, edema fore legs
7/15/28	96	25.6	343.8	9.2	0.484	1,500	Edema spreading
7/16/28	120	24.2	261.0	11.4	0.478	1,500	Edema of scrotum
7/17/28	144	24.0	212.0	12.6	0.486	1,500	Still vomiting
7/18/28	168	24.0	344.8	13.0	0.476	1,500	Vomiting severe, edema neck
7/19/28	192	20.9	405.4	15.8		1,500	Apathy, vomiting, edema less
7/20/28	199						Died in coma during night

TABLE 11—*Data on Dogs in Group VII Following Nephrectomy*

Dog	Duration of Life, Hours	Non-protein Nitro gen, Mg per 100 Cc	Urea Nitro gen, Mg per 100 Cc	Creat- inine, Mg per 100 Cc	Chlor- ides as NaCl, Gm per 100 Cc	Vomit- ing, Hrs	Diarrhea, Hrs	Edema, Hrs	As cites, Hrs	Con vul- sions, Hrs	Ringer's Solu- tion Injected Daily, Cc	
52	201					123	123	0	0	0	1,000	Pulmonary edema
56	165					70	95	0	P M	0	1,000	Pulmonary edema
57	224					115	92	142	190	0	1,000	Pulmonary edema
60	109					49	49	0	0	0	1,500	Pulmonary edema
61	191					68	62	68	168	0	1,500	Pulmonary edema, snuffles
1	199	405.4		15.8	0.471	46	72	48	P M	0	1,500	Pulmonary edema
2	95	218.9		13.9	0.448	0	0	72	0	94	1,500	Pulmonary edema
4	136	254.2	217.9	9.2	0.520	48	72	72	P M	0	1,500	Pulmonary edema
7	161	281.7		11.5	0.511	72	120	120	P M	0	1,500	Pulmonary edema, snuffles

to start with, that the aciduric condition of the gastro-intestinal tract may decrease the absorption of toxic substances, and that the diarrhea may possibly have increased the vicarious elimination

*Histamine*—The animals that were given injections of histamine lived approximately the same time as the controls. The histamine led to a slight temporary decrease or delayed the increase of the nitrogenous constituents in the blood, which was immaterial



The most striking observation in this group was that five of the seven dogs had convulsions. Histamine, when injected in the same amount, does not cause convulsions in normal dogs. We are at a loss for an explanation as to why it caused convulsions in these dogs.

*Magnesium Sulphate*—Magnesium sulphate was used to determine the effect of diarrhea per se. It was shown that these dogs do not live

TABLE 12—Data on Dogs in Group VIII Following Nephrectomy

Dog	Duration of Life, Hours	Vomiting, Hours	Diarrhea, Hours	Edema, Hours	Ascites, Hours	Convulsions	Bicarbonate Ringer's Injected Daily, Cc	
55	133	71	96	0	P M	0	1,000	Pulmonary edema
58	180	118	118	0	165	0	1,500	Pulmonary edema
59	192	146	150	146	160	0	1,500	Pulmonary edema
62	121	54	99	76	P M	0	1,500	
63	185	72	72	72	0	0	1,500	Pulmonary edema
Average 162								

TABLE 13—Data on Dogs in Group IX Following Nephrectomy

Dog	Duration of Life, Hours	Vomiting, Hours	Edema, Hours	Ascites, Hours	Convulsions	Ringer's Solution Injected Daily, Cc	
9	142	96	120	P M	0	1,500	Pulmonary edema, snuffles
10	143	96	72	P M	0	1,000	Snuffles
11	103	94	48	P M	0	1,000	Snuffles
12	118	0	72	P M	0	1,000	Snuffles
13	198	96	144	P M	0	1,500	Snuffles
Average 140							

TABLE 14—Summary of Data on All Groups of Dogs Following Nephrectomy

Group	Procedure	Number of Dogs	Average Life, Hrs	Longest Life, Hrs	Shortest Life, Hrs	Vomiting, Hrs	Diarrhea, Hrs	Numbers		
								Having Salivation	Developing Edema	Having Convulsions
I	Control	6	105.6	140	60	74	75	1	0	0
II	Lactose diet	11	137.6	194	89	73	Before operation	0	0	0
III	Histamine	7	98.7	130	58	74	0	0	0	5
IV	Magnesium sulphate	6	89.0	130	60	46	Before operation	0	0	0
V	Bicarbonate Ringer's *	2	91.0	104	84	48	0	0	0	1
VI	Ringer's	2	65.0	60	62	48	0	0	0	0
VII	Ringer's subcutaneously	9	165.0	224	95	75	73	2	6	1
VIII	Bicarbonate Ringer's subcutaneously	5	162.0	192	121	92	107	0	3	0
IX	Lactose per os and bicarbonate Ringer's subcutaneously	5	140.0	198	103	96	Before operation	2	5	0

\* Solution given intravenously

as long as the controls, and therefore that the diarrhea, per se, has a deleterious effect on the nephrectomized dog. The diarrhea produced by the magnesium sulphate was marked and had an evident weakening effect on the dogs.

*Ringer's Solution Intravenously*—The intravenous administration of Ringer's solution had such a deleterious effect on these dogs, as is shown

by the decreased length of life, that this method was discontinued, especially since an acute pulmonary edema developed in one dog

*Ringer's Solution Subcutaneously*—Our results definitely show that the subcutaneous administration of Ringer's solution prolongs the life of bilaterally nephrectomized dogs, and is the best method that we have employed. We believe that it operates by making up for the water and chlorides lost by vomiting and diarrhea and by aiding vicarious elimination. It is known that the injection of Ringer's solution increases gastric secretion, which, according to McEnery, Meyer and Ivy's work,<sup>1</sup> would tend to decrease nitrogenous retention. The prevention of dehydration and decrease of the sodium chloride, we believe, is the most important factor. The edema per se may prolong life by diluting the toxins in the tissues or by some unknown mechanism.

The production of edema in nephrectomized dogs is especially significant because it has long been a question as to why nephrectomized dogs do not develop edema. According to Bence,<sup>16</sup> nephrectomized rabbits develop edema, and it is known that rabbits do not vomit. Nephrectomized dogs begin to vomit on the second or third day, and diarrhea soon follows, which leads to dehydration and loss of chlorides. The most logical explanation for the appearance of edema in nephrectomized dogs that received Ringer's solution subcutaneously is that the tissues were supplied with water and chlorides so that edema could occur. We are not certain as to the rôle played by the chlorides in the production of the edema. But this problem is under investigation.

#### CONCLUSIONS

1 Control animals on a meat diet live an average of 105.6 hours following double nephrectomy, the maximum length of life being 140 hours and the minimum being sixty hours.

2 Animals on a diet of bread, milk and lactose live an average of 137.6 hours, a maximum of 194 hours and a minimum of eighty-nine hours following double nephrectomy. This is an average of thirty-two hours longer than the control animals. Therefore this diet prolongs life following double nephrectomy and delays the accumulation of nitrogenous constituents of the blood.

3 The injection of Ringer's solution subcutaneously prolongs life following double nephrectomy. The animals in this group live an average of 165 hours, which is sixty hours longer than the postoperative life of the control animals. It also produces an edema, but we are not yet prepared to state whether it is the water or the chlorides that plays the most important part in the production of this edema.

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<sup>16</sup> Bence, N. Experimentelle Beiträge zur Entstehung der nephritischen Oedema, Ztschr. f. klin. Med. 67:69, 1909.

# THE ACTION OF MERBAPHEN (NOVASUROL) ON THE KIDNEY OF THE DOG

A COMBINED FUNCTIONAL AND PATHOLOGIC STUDY\*

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DETROIT

Merbaphen (novasurol), an organic mercury compound, is at present being used as a diuretic in the treatment of certain patients with edema and ascites. It is well known that mercury readily damages the kidney. We<sup>1</sup> have shown that merbaphen, though less toxic than certain other mercurials, in sufficient doses brings about degenerative changes in the renal epithelium of the rabbit identical with that produced by the other less complex mercury compounds in common use.

In this investigation, a further study of the action of merbaphen was made by carrying out combined functional and histologic observations in the dog. Five animals were employed. As shown by MacNider<sup>2</sup> and Dayton,<sup>3</sup> the dog is subject to spontaneous renal disease. To avoid confusion from this factor, the animals were subjected to functional tests and the urine examined before merbaphen was injected. The characteristic lesions of spontaneous nephritis as described by these authors were also searched for when the kidney tissue was examined microscopically.

In a few instances the drug was given directly into the vein, but usually it was injected intramuscularly. It was diluted with physiologic solution of sodium chloride in such proportion that 0.1 cc of merbaphen was contained in 0.5 cc of the solution. Doses varying from 0.045 to 0.332 cc per kilogram or from 0.2 to 0.8 cc per animal were used. Such amounts would be equivalent to from 1 to 2.2 cc for a man weighing 70 Kg. In one instance, a dose of 1.6 cc was given. For varying periods before and after each injection, as indicated in the tables, the

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<sup>2</sup> Johnston, B. I., and Keith, H. M. Toxicity of Novasurol (Merbaphen). Its Action on the Kidney of the Rabbit, *Arch. Int. Med.* **42** 189 (Aug.) 1928.

<sup>3</sup> MacNider, W. de B. A Pathological Study of the Naturally Acquired Chronic Nephropathy of the Dog, *J. M. Research* **34** 177, 1916.

<sup>4</sup> Dayton, H. Reliability of Dogs as Subjects for Experimental Nephritis, *J. M. Research* **31** 177, 1915.

urine was examined microscopically and the volume, albumin, specific gravity and total chlorides determined. The kidney function as evidenced by the phenolsulphonphthalein excretion was observed at frequent intervals. The blood chlorides and either the blood urea nitrogen or the nonprotein nitrogen were determined immediately before the injection and again twenty-four hours afterward. After the animals had been given the drug for different lengths of time, the kidneys were examined either following nephrectomy or at necropsy. Small strips of tissue were removed from different areas of each organ, preserved in 10 per cent formaldehyde, then dehydrated, fixed in paraffin, sectioned and stained with hematoxylin and eosin.

#### PROTOCOLS

Dog 1—An animal weighing 132 Kg was placed in a metabolism cage and given the usual scrap diet and water as desired. Observations were made on the urine and functional state of the kidneys over a preliminary period of twenty-four days. The data are summarized in table 1. There was a trace of albumin in the urine on several occasions, but the results were otherwise normal.

This animal was then given eleven doses of merbaphen over a period of five months at intervals of about two weeks, as shown in table 1. A dose of 0.2 cc was given except in two instances, when 0.1 and 0.4 cc were injected. The first two doses were given intravenously, the remainder intramuscularly. A dose of 0.2 cc in this animal would be 0.015 cc per kilogram and equivalent to approximately 1 cc for a man weighing 70 Kg. Following the first four doses and particularly after the initial one, there was considerable diarrhea, with blood in the stools twice. This did not recur after the later doses, and the dog remained clinically well throughout the experiment. Definite diuresis resulted only following the first and tenth doses. There was no significant change in the specific gravity of the urine. Albumin occurred only occasionally and in small amounts, there being no increase over that present before the experiment was begun. No constant change was observed in the amount of chlorides excreted in the urine during the twenty-four hours following injection of the drug. The ability of the kidneys to excrete phenolsulphonphthalein was not impaired. There was no constant change in the blood chlorides as determined immediately before and twenty-four hours after merbaphen was given. The blood urea nitrogen was within the limits found by Haden and Orr<sup>4</sup> to be normal, except on two occasions, when it rose to 30.4 mg per hundred cubic centimeters of blood.

Seven days after the eleventh dose, the animal was killed within four minutes by a massive dose of ether, and autopsy was immediately performed. The right kidney weighed 38 Gm. The capsule was not thickened and stripped readily, leaving a smooth, glistening, reddish surface. The cut margins did not evert. The cortex and medulla were sharply demarcated. Peripherally, the cortex was a purplish red, whereas medially fine radiating gray lines were separated by narrow reddish areas. The medulla was a dark reddish purple. The pelvis was normal. The left kidney weighed 37 Gm and was similar in appearance to the right kidney.

In small scattered areas, however, the epithelium lining the convoluted tubules was swollen with some loss of cell boundary. The nuclei in some of the cells

4 Haden, R. L., and Orr, T. G. Chemical Changes in the Blood of the Dog After Intestinal Obstruction, *J. Exper. Med.* **37** 365, 1923.

TABLE 1—*The Effect of Merbaphen on the Blood and Urine of Dog 1, Weighing 132 Kg*

Date, 1926	Blood		Water Intake, Cc	Urine				Phenol sul phon phthal ein, per Cent	Total Chloride, Gm (White horn)	Comment
	Urea Nitro gen, Mg per 100 Cc (Mar shall)*	Chloride on Whole Blood, Mg per 100 Cc (White horn)**		Out put, Cc	Albu min Gr ide	Specific Gravity				
2/4 to 2/28			381†	279†	1 or —	1 032§		70	2 18 (4 determi nations)	
3/ 1										Merbaphen, 0.2 cc intravenously
3/ 2			430	490						Mixed with feces and blood
3/ 3			730							Bloody stools
3/ 4			700	610						
3/ 5			530	140	—	1 030				
3/ 6			300	165	—	1 035		—	0 13	
3/ 7	30 1	140		130	—	1 027				
3/ 8		190	650		—	1 028				Diarrheal stools
3/ 9			735	420						
3/10				335	—	1 030				
3/11	20 1	520	300							Merbaphen, 0.1 cc intramuscularly
3/12			100	320	—	1 032			0 41	
3/13			300	165	—					
3/14				190	—	1 023		80	0 32	
3/15				80	—	1 030			0 29	
3/16			400	400	—	1 033				
3/17			250	150	3	1 033				Mixed with feces
3/18			530	210	—	1 035				Merbaphen, 0.2 cc intramuscularly
3/19										Diarrheal stools
3/20			700	215	—	1 036				
3/21			800	310	—	1 026				
3/22			800							Diarrheal stools
3/23			400							Diarrheal stools
3/24			400	200	—	1 028				
3/25								70		
4/10	21 0	340		125	—	1 030				Merbaphen 0.2 cc intramuscularly
4/11	16 3	480	590	151	—	1 038		75	1 01	
4/12			280	240	—	1 038			2 30	
4/13				27						
4/24	30 1	490		175		1 040				Merbaphen, 0.2 cc intramuscularly
4/25	13 5	400						80		
5/ 2										Merbaphen 0.4 cc intramuscularly
5/16										Merbaphen, 0.2 cc intramuscularly
5/17			385	280	—	1 042		80	1 59	
5/18			225	135	—	1 038			0 88	
5/19				175	1	1 040			1 15	
5/20				55	—	1 029				
5/30	16 3	500								Merbaphen 0.2 cc intramuscularly
5/31	14 0	420	300	224	—	1 036		85	0 33	
6/ 1			250	121	—	1 029			1 02	
6/ 2			110	137	—	1 039			0 79	
6/12				142	—	1 037			0 99	
6/13	7 9	400	660	415	—	1 028			5 39	Merbaphen, 0.2 cc intramuscularly
6/14	17 3			150	—	1 035		80	1 05	
6/15			720	475	—	1 032			8 40	
6/16			160	350	—	1 026			4 09	
6/17				120	2	1 043			1 03	
6/18			250	187	1	1 046			1 65	
6/19					2	1 044				
6/16			140	85	3				0 90	
6/17			220	110	3	1 051			0 50	
6/18			270	110	3	1 035			0 46	
6/19					3	1 060				
6/24					—	1 028				
6/27	13 5	500	340	240	—	1 049			1 75	Merbaphen, 0.4 cc intramuscularly
6/28	18 2	510	345	100	2	1 039		90	0 45	
6/29			565	295	—	1 041			3 19	
6/30			260		2	1 046				
7/ 1			305	52	2	1 014			0 32	
7/ 2			475	230	1	1 033			2 14	
7/10			390	150	1	1 035			0 64	
7/11	11 2	490	325	130	—	1 053			0 52	Merbaphen, 0.4 cc intramuscularly
7/12	10 7	510	260	175	—	1 044		80	0 76	
7/13			375	290	—	1 042			4 10	
7/14			170	105	2	1 042			1 53	
7/15				225	—	1 042				
7/16			310	100	—	1 052			0 89	

\* Van Slyke, D. D., and Cullen, G. E. Modification of Marshall's Method, J. Biol. Chem. 19 211, 1914

\*\* Whitehorn J. Biol. Chem. 45 449, 1921

† Control average of eighteen determinations—24 hour periods, minimum, 75 cc, maximum, 550 cc

‡ Control average of fourteen determinations—24 hour periods, minimum, 73 cc, maximum, 575 cc

§ Control average of nine determinations—24 hour specimens, minimum, 1 036, maximum, 1 048

had disappeared. There was a small amount of exudate in the lumina of a number of the convoluted tubules. The malpighian bodies were normal. There was no evidence of edema, no increase in connective tissue and no infiltration with small round cells. A few small retention cysts were scattered throughout the cortex.

*Summary*—Dog 1 did not have abnormal functional or histologic manifestations to classify it as nephropathic, although there were traces of albumin in the urine on the preliminary examination. This animal was given eleven doses of merbaphen, each equivalent to approximately 1 cc for a man weighing 70 Kg over a period of five months. Diarrhea was present after the first four doses, but there was no further clinical evidence of toxicity. There was no constant diuresis, no decrease in the specific gravity, no increase in the albumin in the urine, and no constant increased output of chlorides. There was no diminution in the amount of phenolsulphonphthalein excreted at the end of two hours, and no constant change in the blood urea nitrogen or blood chlorides. The kidneys when examined seven days after the eleventh dose of the drug showed no gross change. Microscopically, there was evidence of a small amount of acute degeneration.

Dog 2—An animal weighing 148 Kg was studied in a similar manner, except that larger doses of merbaphen were given. Observation prior to injection of the drug revealed no abnormality. The clinical observations were similar to those in dog 1.

Twelve injections of merbaphen were given over a period of about five months at intervals of two weeks. A dose of 0.4 cc was given except in three instances when on two occasions 0.2 cc was injected and once, 0.8 cc. The first dose was given intravenously, the remainder intramuscularly. A dose of 0.4 cc in this animal would be 0.024 cc per kilogram and equivalent to 1.7 cc for a man weighing 70 Kg. Bloody diarrhea was observed following the first dose and simple diarrhea after the early injections. The animal otherwise remained clinically well. Definite diuresis was observed only following the second and seventh doses. There was no significant change in the specific gravity of the urine. Albumin did not appear until following the last four doses, when the urine contained a moderate amount. The chloride excretion was determined following seven injections. In only two instances was there a definite increase, and this occurred during the second twenty-four hours. The phthalein excretion, which had been 80 per cent at the end of two hours before the experiment was begun, was repeatedly determined. It varied between 60 and 90 per cent, the last two determinations being 90 and 80 per cent, respectively. The test was usually carried out during the twenty-four hours following the injection of the drug, but a number of observations were made at other times to note any variation. There was no constant change in the blood urea nitrogen or blood chlorides. The former reached a level of 27.9 on one occasion, six days after the initial dose of merbaphen.

Nine days after the twelfth dose of the drug, the animal was killed within four minutes by a massive dose of ether, and autopsy was immediately performed. The kidneys each weighed 40 Gm and were similar in appearance. The capsule was not thickened and stripped readily, leaving a smooth, glistening, dark red surface. The cortex and the medulla were sharply demarcated. The cut margins did not evert. The cortex was dark red peripherally but medially contained light lines separated by narrow reddish areas. The pyramids were dark purplish red. The pelvis and arteries were normal.

When examined histologically, a portion of the convoluted tubules, especially those in close proximity to malpighian bodies, showed a mild degree of degenera-

tion There was some swelling of the epithelium and loss of cell boundary The nuclei were for the most part intact There was considerable flattening of the epithelium in some of the tubules The lumina contained considerable homogeneous pinkish-staining exudate Similar exudate was present in the capsular spaces of a few of the malpighian bodies The remainder were normal There was no evidence of edema An occasional small area showing dense infiltration with round cells and increase in connective tissue with disappearance of the tubules was found In these areas, the malpighian bodies had thickened capsules and partially fibrosed glomeruli Such areas were small and were found only after careful search The blood vessels were normal There were a few small, cystlike spaces

*Summary*—Although a few small areas of chronic change were found histologically, since there was no albumin in the urine and functional tests were normal, dog 2 could scarcely be classified as nephropathic This animal was given twelve injections of merbaphen, each being equivalent to 17 cc for a man weighing 70 Kg, over a period of five months at intervals of two weeks There was some diarrhea and melena following the initial doses, but except for this the dog remained clinically well Following the last four doses, albumin appeared in the urine The phthalein excretion and the specific gravity of the urine remained normal No constant change was observed in the blood urea nitrogen and chlorides or urine chlorides, and diuresis was not constant At necropsy, nine days after the twelfth dose, a small amount of parenchymal damage and a small amount of chronic change were present

Dog 3—An animal weighing 27.3 Kg was studied in a similar manner Still larger doses were given The preliminary phthalein excretion at the end of two hours was 80 per cent, and the urine was normal

Five doses of 0.8 cc were given over a period of three months at intervals of two weeks This dose would be 0.029 cc per kilogram and equivalent to 2.05 cc for a man weighing 70 Kg All injections were made intramuscularly Following the first dose there was considerable diarrhea, malaise, frothing at the mouth and grinding of the teeth This disappeared in a few days and did not recur following subsequent doses There was some diuresis after each dose This was greatest following the second and third doses and was accompanied by a greatly increased intake There was no significant change in the specific gravity of the urine Albumin was present in the urine after each dose, being found from the second to the fourth days following injection of the drug The phthalein excretion remained high, and the blood urea nitrogen was not increased There was an increase in the urine chloride on three occasions, but on two of these it was delayed twenty-four hours There was no constant change in the blood chlorides

Seven days after the fifth dose, nephrectomy of the left kidney was done with the dog under ether anesthesia (This animal was subsequently used for other purposes) The left kidney weighed 60 Gm The capsule stripped with slight difficulty, some of the tissue being torn from the otherwise smooth reddish surface The cut margins everted slightly The cortex and medulla were fairly sharply demarcated The inner half of the former showed definite yellowish lines radiating outward and separated by narrow reddish areas continuous with the outer reddish portion The medulla was a purplish color The vessels and pelvis were normal

On histologic examination, certain areas of proximal convoluted tubules took the acid stain more deeply than the remainder of the tissue Here the epithelial cells were swollen, the cell boundary indistinct and the nucleus was occasionally absent There was considerable exudate in the lumina There was no evidence

of edema and no increase in connective tissue or infiltration with wandering cells. The malpighian bodies and blood vessels were normal. An occasional small cyst was present.

*Summary*—Dog 3, a normal animal, was given five doses of merbaphen, each equivalent to 2.05 cc for a man weighing 70 Kg, over a period of three months. She showed diarrhea and malaise after the first dose but soon recovered and remained clinically well. Diuresis occurred after each dose, and albumin appeared in the urine after the last four. The blood urea nitrogen, phthalein excretion and specific gravity of the urine remained normal. An increased output of chlorides in the urine took place on three occasions. There was no constant change in the blood chlorides. The left kidney, removed at operation seven days after the fifth dose of merbaphen, showed evidence of some acute degeneration.

Dog 6—An animal weighing 19 Kg was given four doses of 0.6 cc of merbaphen over a period of one and a half months at intervals of two weeks. This dose would be 0.032 cc per kilogram and equivalent to 2.21 cc for a man weighing 70 Kg. The first dose caused diarrhea and considerable malaise. This soon disappeared and did not recur. A definite diuresis occurred after the first dose, but there was no definite increased output after subsequent doses. The specific gravity showed no significant change. There was no albumin following the first dose, but it was present in considerable quantities following later doses. The phthalein excretion remained high, and the blood urea nitrogen was not increased. There was an increase in the urine chlorides on two occasions. There was no constant change in the blood chlorides.

Four days after the fourth dose, nephrectomy of the left kidney was performed with the animal under ether anesthesia. The animal died twelve hours later from hemorrhage into the peritoneal cavity. Autopsy was done four hours later and the right kidney removed and examined.

The left kidney weighed 48 Gm. The capsule was slightly thickened but stripped fairly readily, the surface being torn in only a few places. The surface was otherwise smooth and was a reddish yellow. On cut section, the margins everted slightly. The cortex was sharply demarcated from the purplish medulla. The peripheral portion of the cortex was reddish brown, while the deep portion consisted of yellowish radiating lines separated by narrow reddish areas. The blood vessels and pelvis were normal.

On histologic examination the convoluted tubules showed evidence of degeneration, more widespread and involving a greater proportion of the parenchyma than in dogs 1, 2 and 3. Although there was little evidence of necrosis, the degeneration was more advanced. In addition to the swelling and loss of cell boundary, many of the nuclei were pyknotic and in a great many cells had disappeared. There was considerable exudate in the lumina. The majority of the malpighian bodies were normal. In a few there was a small amount of exudate in the capsular space. There were a few wedged-shaped subcapsular areas showing infiltration with round cells and increased connective tissue. In these, Bowman's capsule and the glomeruli had undergone some fibrosis. There were a few cyst-like spaces. The blood vessels were not abnormal.

The right kidney which was removed at autopsy showed extensive parenchymatous degeneration. About three fourths of the convoluted tubules and about one half of the ascending limbs of Henle had undergone complete necrosis. There was also swelling and vacuolization in the collecting tubules. Few normal convoluted tubules remained. Those not already completely necrosed were in the various stages of degeneration. The tubules were widely separated. Except for a small amount of exudate and fibrosis, as seen in the left kidney, the malpighian



bodies were not abnormal. A few wedge-shaped subcapsular areas of increased connective tissue and round cell infiltration were present in this kidney, as in the left. The blood vessels were not abnormal.

This dog, although apparently normal clinically, must be considered at least mildly nephropathic as evidenced by histologic examination of the kidneys after nephrectomy and at necropsy. She was given four doses of 0.6 cc of merbaphen

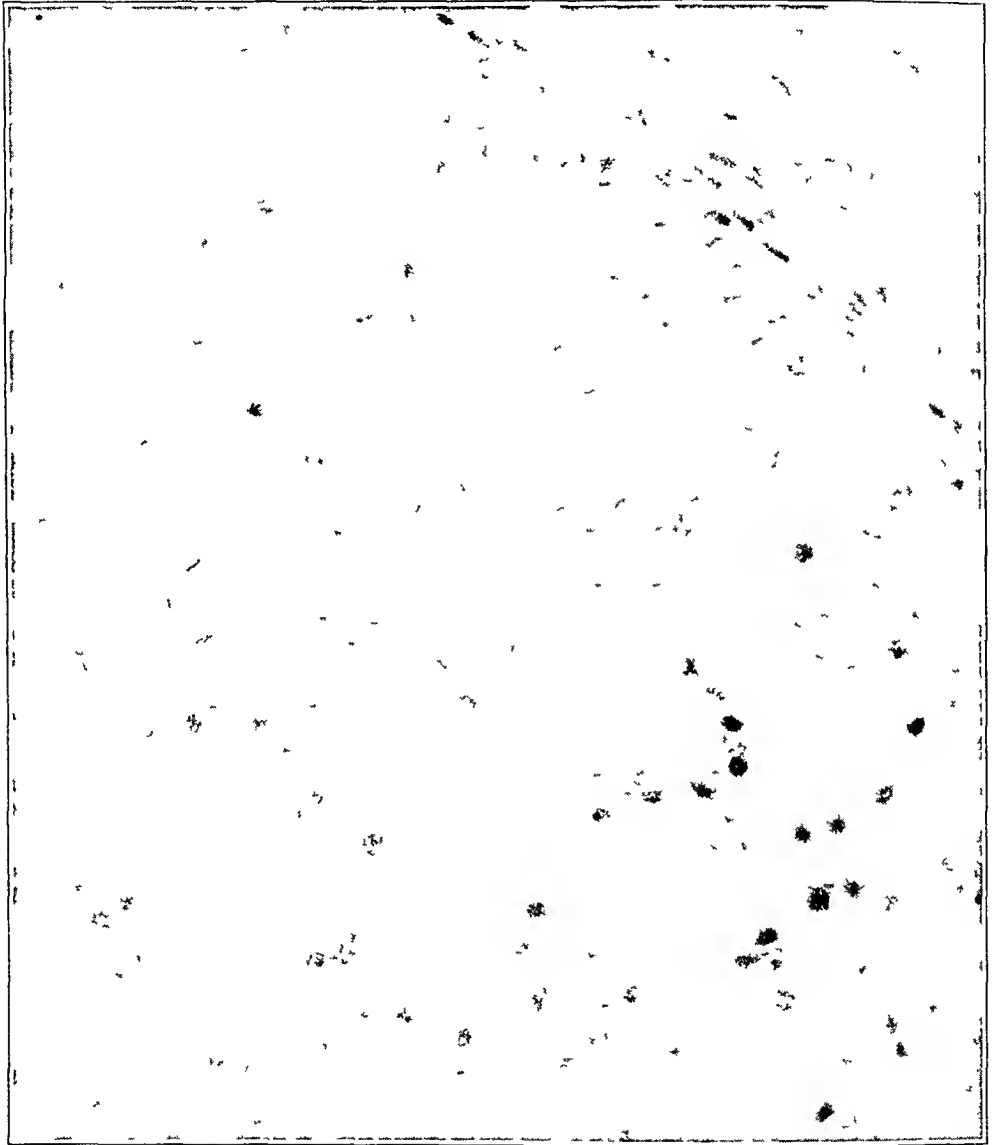


Fig 1—Section from the left kidney of dog 6 removed at operation four days after the fourth dose of 0.032 cc per kilogram of merbaphen given intramuscularly. In the center of the photograph, the convoluted tubules show characteristic degeneration. The cytoplasm has partially disintegrated and that remaining has taken the acid stain more deeply than the surrounding normal tissue. The nuclei are pyknotic and the lumina are almost completely filled with debris, 16 mm obj.

over a period of one and one-half months. Such a dose would be equivalent to 2.2 cc for a man weighing 70 Kg. Diarrhea occurred after the first dose, and considerable albumin appeared in the urine after the last three doses. No diuresis was observed, and there was no constant increase in the total chlorides in the urine during the twenty-four hours following the injection of the drug. There was no constant change in the blood chlorides. The blood urea nitrogen, phthalein excretion and specific gravity of the urine remained unchanged. The left kidney removed at operation four days after the fourth dose showed a definite amount of early parenchymatous degeneration. The right kidney removed at autopsy sixteen hours later showed extensive tubular change. There was a small amount of chronic renal change.

**Dog 7**—An animal weighing 13.2 Kg. was placed in a metabolism cage and given 320 Gm. of dog biscuit daily with water as desired. For a preliminary period of five days, the water intake and urine output were carefully determined every twelve hours. Urinalysis was carried out on each specimen and the total chlorides estimated. The blood on three occasions was examined for nonprotein nitrogen and chlorides. These preliminary results are recorded in table 2. The average intake for twelve hours was 154 cc. and the urine output, 156 cc. The average total chloride in the twelve hour urine was 0.78 Gm. A trace of albumin was found in all specimens and an occasional cast on one examination.

The animal was now given 0.3 cc. of merbaphen intramuscularly on three occasions at intervals of two and three weeks, respectively. This dose would be 0.023 cc. per kilogram and equivalent to 1.9 cc. for a man weighing 70 Kg. Before and after each injection detailed observations, summarized in table 2, were carried out every twelve hours as in the preliminary study. There was a definite diuresis on each occasion. The specific gravity showed no significant change. The albumin persisted in the urine but was not increased in amount. After the second dose a trace of reducing substance appeared in the urine. There was a slight increase in the total chlorides after one injection, but there was no constant change in the blood chlorides or nonprotein nitrogen.

One week after the third injection, a further investigation was carried out on the same animal. The twenty-four hour period was divided into three periods of eight hours each and the drug given at the beginning of the second period in the manner described by Keith and Whelan<sup>5</sup>. No food or water was given for the twenty-four hours. The dog was catheterized at the beginning of the experiment and at the end of each eight hours. The dose given was 0.3 cc. or 0.023 cc. per kilogram. Three similar separate investigations were carried out, as outlined in table 3. After each dose of merbaphen, definite diuresis occurred accompanied by an increase in the output of total chlorides. No increase in the albuminuria and no showers of casts were noted. The reducing substance persisted in the urine and increased slightly in amount.

The dog was now allowed to rest for four months, at the end of which time nephrectomy of the left kidney was done under ether anesthesia and the kidney examined. Microscopically there was no evidence of acute degeneration, but in some of the tubules the epithelium was a little flatter than normal. The glomeruli and blood vessels were normal. There were occasional small nests of lymphocytic infiltration and an occasional small cyst.

The animal was again allowed to rest, this time for a period of six weeks. During the next five and one-half weeks she was given frequent doses of mer-

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<sup>5</sup> Keith, N. M., and Whelan, Mary. A Study of the Action of Ammonium Chloride and Organic Mercury Compounds, *J. Clin. Investigation* **3** 149, 1926.

TABLE 2—The Effect of Merbaphen on the Blood and Urine of Dog 7, Weighing 132 Kg

Blood			Urine, 12 Hour Specimens										Comment
Nonprotein Plasma Nitrogen, Chloride, Mg per Mg per 100 Cc * 100 Cc (Folin (Van and Wu) Slyke)†			Water Intake, Cc	Output, Cc	Specific Gravity	Albumin, Grde	Sugar, Gm	Blood Gm	Total (Van Slyke)† Chloride, Gm	Microscopic Examination			
Date, 1926- 1927			Time										
12/15	35.4	595	9 p m	115	137	1.020	Trace	0	0	0.60	Negative	Diet, 320 Gm of dog biscuit daily	
12/16			9 i m	130	190	1.021	Trace	0	0	0.93	Negative		
12/17	36.6	643	9 a m	140	215	1.025	Trace	0	0	0.59	Negative		
12/18	41.1	582	9 p m	201	145	1.020	Trace	0	0	1.00	Negative		
12/19			9 i m	130	165	1.023	Trace	0	0	0.93	Negative	Merbaphen, 0.3 cc intramuscularly	
12/20			9 a m	140	Lost	1.027	Trace	0	0	0.69	Three granular casts, white blood cells		
12/21	36.2	559	9 a m	250	140	1.028	Trace	0	0	0.54	Few white blood cells		
12/22	38.6	482	9 p m	185	145	1.024	Trace	0	0	0.79	Oxalates and urates		
12/23	40.6	606	9 p m	100	390	1.017	Trace	0	0	0.26	Negative	Merbaphen, 0.3 cc intramuscularly	
12/24			9 a m	90	85	1.016	Trace	0	0	0.62	Negative		
12/25			9 a m	250	125	1.026	Trace	0	0	0.36	Few white blood cells		
12/26			9 p m	125	186	1.030	Trace	0	0	0.63	Few white blood cells		
12/27			9 p m	250	155	1.030	Trace	0	0	0.52	Negative	Phenolsulphophthalein, 65 per cent	
12/28			9 p m	155	128	1.028	Trace	Trace	0	1.15	Negative		
12/29			9 a m	65	187	1.038	Trace	Trace	0	1.61	Negative		
12/30	37.5	577	9 p m	165	165	1.038	Trace	Trace	0	0.64	Few pus cells		
12/31			9 a m	200	320	1.015	1	0	0	1.77	Negative	Merbaphen, 0.3 cc intramuscularly	
12/32			9 p m	100	233	1.010	1	0	0	0.31	Negative		
12/33			9 a m	230	257	1.025	Trace	0	0	0.37	Negative		
12/34			9 p m	180	96	1.025	Trace	0	0	0.21	Negative		
12/35	34.8	630	9 a m	115	236	1.023	Trace	Trace	0	1.77	Negative	Merbaphen, 0.3 cc intramuscularly	
12/36			9 p m	160	115	1.039	Trace	1+	0	1.04	Many pus cells		
12/37			9 a m	50	118	1.030	1	Trace	?	0.95	Many red blood cells, 2 casts, white blood cells		
12/38	37.2	555	9 p m	80	185	1.031	?	?	0	1.65	Few white blood cells		
12/39			9 a m	200	356	1.029	?	0	?	1.79	Red and white blood cells, epithelial cells	Phenolsulphophthalein, 54 per cent	
12/40	47.2	615	9 p m	140	110	1.034	?	Trace	0	0.46	Many pus cells		
12/41			9 a m	215	130	1.023	Trace	?	0	0.33	Red blood cells, white blood cells, epithelial cells		
12/42			9 p m	60	112	1.034	?	Trace	0	0.12	Red blood cells, white blood cells		
12/43			9 a m	93	118	1.026	Trace	?	0	0.75	Few red blood cells and white blood cells		
12/44			9 p m			1.027	Trace	?	0	0.61	Few red blood cells and white blood cells		

\* Folin and Wu J Biol Chem 38 81, 1919

† Van Slyke J Biol Chem 58 523 1923 1924

baphen, at first every three to five days, and later every other day. In all, fourteen doses of 0.3 cc or 0.023 cc per kilogram were given and observations carried out as outlined in table 4. During the first three weeks diuresis occurred after each injection, except the second. Later this was not so pronounced, although the average daily output was increased from approximately 260 to 408 cc. Albumin persisted, with little change in the amount. The reducing substance remained constantly in the urine in measurable amounts. After the fourth injection casts appeared, and following later doses, they gradually increased in number. Following nine of the fourteen injections, the total chlorides were increased, after two, the specimens were lost, and after three, they were the same or decreased. The blood nonprotein nitrogen was somewhat above normal on three occasions and within normal limits on three. The elevation was not marked and was possibly due to the fact that the remaining kidney was slightly overtaxed by repeated doses of the drug. Three months after the completion of the experiment the nonprotein nitrogen was normal on two occasions, demonstrating the absence of

TABLE 3—*The Effect of Merbaphen on the Urine of Dog 7, Weighing 13.2 Kg \**

Date, 1927	Time	Urine					Microscopic Examination	Comment
		Out- put, Cc	Specific Gravity	Albu- min, Grade	Reduc- ing Sub- stance	Chloride, Gm (Van Slyke)†		
1/30	11 p m							Catheterized Merbaphen, 0.3 cc intramuscularly
1/31	7 a m	51	1.048	Trace	1	0.40	Many pus cells	
	3 p m	75	1.039	Trace	Trace	1.30	Pus cells and erythrocytes	Catheterized Merbaphen, 0.3 cc intramuscularly
	11 p m	41	1.042	1	Trace	0.43	Pus cells and erythrocytes	
2/16	11 p m							
2/17	7 a m	57	1.051		2	0.49	Few erythrocytes	
	3 p m	92	1.033	Trace	3	0.70	Many erythrocytes	Catheterized Merbaphen, 0.3 cc intramuscularly
	11 p m	42	1.036	Trace	Trace	0.27	Many erythrocytes, some leukocytes	
3/ 9	11 p m							
	7 a m	60	1.055		3	0.83	Erythrocytes, leukocytes	
	3 p m	74	1.040	Trace	2	1.37	Erythrocytes, leukocytes	
		44	1.040	Trace	2	0.15	Erythrocytes, leukocytes	

\* During these experiments the dog received no food or water. All specimens of urine were obtained by catheter.

† Van Slyke J Biol Chem 58: 523, 1923-1924.

permanent renal injury. During the final two weeks of the experiment, the dog refused some of her diet and was much less active than usual. There was no vomiting.

For the next five months, she was given a general hospital scrap diet, and at the end of this period weighed 17.5 Kg and appeared well. The urine contained no albumin, sugar or casts. The dog was again placed in a metabolism cage and given no food or water for twenty-four hours. She was catheterized before the experiment was begun and at the end of each eight hours. At the end of the first eight hours, she was given a dose of 1.6 cc of merbaphen intramuscularly. Such a dose would be 0.09 cc per kilogram and corresponds to that which we<sup>1</sup> found to be the maximum single tolerated dose for a normal rabbit. This resulted in a marked diuresis with a great increase in the total urine chlorides, as shown in table 5. During the third eight hours, there were showers of finely granular and cell casts in the urine. No reducing substance was noted. About thirty-six hours after the drug was given the animal vomited, became drowsy and weak, and passed numerous soft and liquid stools. The vomiting and malaise increased, and after five days the dog died. Autopsy was performed immediately.

TABLE 4—The Effect of Merbaphen on the Blood and Urine of Dog 7, Weighing 14.1 Kg

Date, 1927	Blood				Urine			Microscopic Examination	Comment
	Nonprotein Nitrogen, Mg per 100 Cc	Plasma Chloride, Mg per 100 Cc	Water Intake, Cc	Output Cc	Specific Gravity	Albumin, Grade	Reducing Substance, Gm	Total (Van Slyke) Gm	
7/7	56.1	381	110	425	1.025	Trace	1	4.14	Merbaphen, 0.3 cc intramuscularly
7/8			100	128	1.057	Trace	2	0.99	Diet, 320 Gm dog biscuit daily
7/9			110	126	1.049	—	0.45	1.36	
7/10			140	173	1.043	—	1	2.35	Merbaphen, 0.3 cc intramuscularly
7/11			260	329	1.028	2	1	2.61	
7/12				310	1.023	Trace	1	2.17	
7/13			210	142	1.044	Trace	0.36	1.37	
7/14			115	145	1.050	Trace	1	1.76	
7/15			235	158	1.032	—	0.46	1.91	
7/16			65	420	1.026	Trace	0.06	3.91	
7/17			240	130	1.049	—	1	0.78	
7/18			?	272	1.031	—	1	1.90	
7/19			?	238	1.010	1	1	1.78	
7/20			70	350	1.031	—	?	3.55	
7/21	64.6	581	90	173	1.049	—	1	1.28	
7/22			30	370	1.030	—	1	3.15	
7/23			410	166	1.041	Trace	1	0.90	
7/24			115	347	1.039	Trace	0.96	2.81	
7/25			80	420	1.030	Trace	1	2.55	
7/26	29.0			365	1.033	Trace	0.61	1.35	
7/27			385	350	1.038	1	2	0.71	
7/28			295	Lost					
7/29	32.6		280	330	1.033	2	2.75	0.91	
7/30			435	425	1.024	1	1.77	1.42	
7/31			210	420	1.032	1	2.14	0.75	
8/1			410	350	1.020	1	1	0.83	
8/2				330	1.025	Trace	1.61	1.02	
8/3			400	338	1.020	1	0.99	0.53	
8/4			270	365	1.025	Trace	1	1.13	
8/5	38.5	500	400	390	1.014	Trace	Trace	1.54	
8/6			310	355	1.015	Trace	1	0.72	
8/7			145	350	1.029	Trace	1	1.62	
8/8			?	Lost					
8/9			120	433	1.020	—	1	2.26	
8/10				487	1.018	Trace	Trace	1.86	
8/11			265	615	1.015	Trace	Trace	2.42	
8/12			550	475	1.017	1	Trace	1.87	
8/13	55.0	616		540	1.017	1		1.93	
11/1	32.0								
11/30	42.8								

\* Folin and Wu J Biol Chem 38 81 1919

† Van Slyke J Biol Chem 18 523 1923 1924

The left kidney had been previously removed. The right kidney was pale and small but smooth, and the capsule stripped readily. The cut edges rolled out slightly. The cortex was uniformly pale. The medulla was a chocolate red.

On histologic examination, there was widespread parenchymatous degeneration. The majority of the convoluted tubules and ascending limbs of Henle had undergone complete necrosis. The remainder showed various stages of degeneration.



Fig 2—Section from the right kidney of dog 7 removed at autopsy five days after a single lethal dose of merbaphen. The glomeruli are normal. The epithelium of the convoluted tubules for the most part shows either complete necrosis or the various stages of regeneration, 16 mm obj.

A good deal of exudate and a large number of casts were present in the lumina. The malpighian bodies were normal except that a few showed a little homogeneous exudate in the capsular space. There was some evidence of edema. Considerable regeneration was found, as evidenced by the presence of large irregular

cells with vesicular nuclei and bluish-staining cytoplasm. In some areas, the necrotic material was surrounded by irregular young cells. Some of the tubules were lined by flattened epithelium, although this was not a prominent feature. No calcium deposition was seen. As described in the left kidney, there were a few small areas of lymphocytic infiltration and a number of small cysts.

*Summary*—Dog 7 was used for a number of different experiments during which the diet was carefully controlled. A trace of albumin was found in the urine before the study was begun, but nothing further was found to classify the animal as nephropathic. In the first experiment, three doses of 0.3 cc of merbaphen were given at rather long intervals. Following each injection there was diuresis, and after one, an increased chloride output in the urine. A trace of reducing substance appeared in the urine, but no other evidence of toxicity was observed. There was no constant change in the blood chlorides.

One week after the first experiment, a second, similar to the first except that no food or water was given for twenty-four hours, was started. A dose of 0.3 cc was given on three separate occasions, at considerable intervals. A definite

TABLE 5—*The Effect of Merbaphen on the Blood and Urine of Dog 7, Weighing 17.5 Kg*

Date, 1928	Time	Out put, Cc	Specific Gravity	Albu min, Grade	Urine		Microscopic Examination	Comment
					Reduc ing Sub stance	Total Chloride, Gm (Van Slyke)*		
3/27	11 p m			—	0		Red and white blood cells, no casts	
3/28	7 a m	113	1.043	2		0.97	Red and white blood cells, no casts	Merbaphen, 1.6 cc intramuscularly
3/28	3 p m	715	1.013	1	0	6.30	Red and white blood cells, no casts	
3/28	11 p m	82	1.024	2	0	0.47	Shower of finely granular casts, red and white blood cells	
4/ 2				2	0		Red and white blood cells, no casts	

\* Van Slyke. J. Biol. Chem. 58: 523, 1923-1924.

diuresis and increased output of chlorides resulted following each injection. There was no evidence of toxicity except that the reducing substance increased in amount.

Four months later, the left kidney was removed under anesthesia and when examined microscopically did not show acute degeneration.

After a further rest of six weeks, fourteen doses of 0.3 cc were given at short intervals over a period of about one and one-half months. Except following the last few doses, a definite diuresis and an increased chloride excretion occurred. Signs of toxicity appeared toward the end of this experiment in the form of general malaise and increased albumin and casts in the urine.

During the next five months, the animal was allowed to rest and at the end of that time appeared well. A single dose was now given which, although a marked diuresis and increased chloride excretion had occurred, proved lethal five days later. At autopsy, extensive tubular degeneration with considerable evidence of regeneration was found.

## COMMENT

Saxl and Heilig<sup>6</sup> Nonnenbruch,<sup>7</sup> Muhling<sup>8</sup> and others have shown that merbaphen produces a relative and absolute increase in the urine chlorides both in normal patients and in those with edema. Keith and Whelan<sup>9</sup> have confirmed these observations and have also found this to be true in the dog. Crawford and McIntosh<sup>10</sup> expressed the belief that the increase in chloride output persists longer than the diuresis. In this study in dogs 1, 2, 3 and 6, we did not find a constant increased chloride excretion in the urine following the injection of merbaphen. In these animals, however, the chloride intake was not controlled. In dog 7, in which a constant diet was maintained, the chloride excretion following the injection of merbaphen was always increased. Various writers have found diuresis to be inconstant in the normal subject. In our experiments an increase in urine output following the injection of merbaphen occurred only when the fluid intake was limited or when no fluid was given. Crawford and McIntosh<sup>10</sup> found that in human patients studied by them there was a definite lowering of the plasma chlorides at the end of four and one-half hours. Other observers have not found such constant changes. Keith and Whelan<sup>5</sup> reported that the changes in concentration of the blood chlorides following injection of merbaphen are variable and never marked in degree. They found no change in the carbon dioxide combining power and no significant change in the non-protein nitrogen of the blood. In this study, no constant changes were found in the blood chlorides when examined twenty-four hours after injection of the merbaphen.

The doses used per kilogram were comparable to amounts used therapeutically in man, except in one instance. This was in dog 7, that was given 1.6 cc, which proved lethal. This was 0.09 cc per kilogram and equivalent to 6.3 cc for a man weighing 70 Kg. Except in one experiment, the intervals between doses were somewhat longer than those allowed as a rule when the drug was used as a diuretic. In this one exception, the interval was reduced to as short as one day over a period of about five weeks.

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6 Saxl, P., and Heilig, R. Ueber die diuretische Wirkung von Novasurol und anderen Quecksilber Injectionen, *Wien klin Wchnschr* **33** 943, 1920.

7 Nonnenbruch, W. Ueber die Wirkung des Novasurols auf Blut und Diurese, *Munchen med Wchnschr* **68** 1282, 1921.

8 Muhling, A. Studie ueber die diuretische Wirkungsweise von Quecksilber, ausgefuhrt mit dem organischen Quecksilberpreparat Novasurol, *Munchen med Wchnschr* **68** 1447, 1921.

9 Keith and Whelan (footnote 5). Keith, N. M., and Whelan, Mary. The Effect of Novasurol on the Composition of Blood and Urine, *Am J Physiol* **72** 195, 1925.

10 Crawford, J. H., and McIntosh, J. Observations on the Use of Novasurol in Edema Due to Heart Failure, *J Clin Investigation* **1** 333, 1925.



Bloody diarrhea and malaise were observed occasionally after the initial doses, but this was not seen subsequently unless the drug was given in large amounts or at short intervals. Albumin was found after the larger doses, especially if repeated. It was definitely increased in three instances, namely, in dog 6 after the last three doses, each of which was 0.6 cc, in dog 7 after several doses of 0.3 cc repeated at short intervals, and again in dog 7 after the lethal dose of 1.6 cc. In the last two instances, albumin was accompanied by casts. When the animal was allowed to rest, signs of toxicity and renal irritation quickly disappeared. A reducing substance was present in the urine of dog 7 following the later doses.

As evidenced by the phthalein excretion, blood urea or nonprotein nitrogen, and the specific gravity of the urine, no chronic functional renal damage could be demonstrated even after the drug had been given over a period of five months.

Examination of the kidneys of those animals to which merbaphen had been given in repeated doses, and at intervals corresponding to what is recognized as correct therapeutically for man, showed slight parenchymatous change. Such kidneys were examined from three to nine days after the final dose of the drug. There was also found considerable exudate in the lumina. In dog 7, when the kidney was not examined for four months after the administration of merbaphen, no degenerative change was present. In dog 6 the right kidney was removed at autopsy following death due to intraperitoneal hemorrhage. The extensive degeneration found is considered to be due to the combined action of merbaphen, ether and postmortem change in an already damaged kidney.

Dog 7 died five days following a dose of 1.6 cc. This amounted to only 0.09 cc per kilogram. We<sup>1</sup> found this amount to be the maximum single tolerated dose per kilogram in the normal rabbit. At this time, however, dog 7 possessed only one kidney and six weeks previously had been given repeated large doses of merbaphen. These factors doubtless explain the small amount necessary to produce death in this animal. It is interesting to note that following this lethal dose marked diuresis and an increased output of urine chlorides occurred.

The right kidney of dog 7, removed immediately after death, showed extensive tubular damage. There was almost complete necrosis of all the convoluted tubules and ascending limbs of Henle, with little change in the glomeruli. Considerable evidence of regeneration was present but no calcium deposition. The histologic picture seen in this kidney corresponds closely with that seen in the kidney of the rabbit dying from a single lethal dose of merbaphen.

The early changes described in the other kidneys are also similar to those seen in the kidney of the rabbit when small doses have been given. Lazarus-Barlow<sup>11</sup> observed similar early degenerative changes in rabbits killed three days after three doses of 0.2 cc of merbaphen given at intervals of three days. MacNider<sup>2</sup> pointed out how readily renal epithelium, especially that which is already the seat of slight degeneration, undergoes further change early after death. The tissue used in this study was removed at operation or immediately after death and preserved at once in 10 per cent formaldehyde. It is thus improbable that autolytic change in the parenchyma brought about this slight degeneration. It is known that ether will injure the tubular epithelium of the kidney, and albumin and casts are commonly found in the urine for from one to three days following anesthesia. MacNider<sup>12</sup> showed that in the normal dog after morphine-ether anesthesia lasting from two and one-half to three hours the kidney parenchyma is normal histologically. In the naturally nephropathic animal, however, under similar circumstances some parenchymatous degeneration is often found, especially if the dog is first given uranium nitrate and then placed under the anesthetic.

It is possible that mercurials in conjunction with ether might have a similar effect. It is doubtful, however, whether ether given for four minutes could produce demonstrable degeneration in the kidney even when given in conjunction with merbaphen. On the other hand, when nephrectomy was done ether was used as an anesthetic over a period of about one hour. It is conceivable that in such instances degenerative changes might have been made more extensive by ether. That such a result, if present, must be slight is borne out by the entire absence of degeneration in the left kidney of dog 7 removed by nephrectomy.

It is accordingly felt that the renal degeneration present, together with the casts and exudate in the lumina, is direct evidence of the toxic effect of merbaphen on the tubular epithelium. There is little doubt that such change is readily repaired in the normal subject provided suitable rest periods are given and the doses used are not too large. No evidence was found to prove that any chronic change resulted from the continued use of the drug. The chronic changes described could not be attributed to merbaphen but were probably spontaneous. MacNider<sup>2</sup> considered only those dogs nephropathic which prior to autopsy showed albumin intermittently or constantly in the urine together with various types of casts and at autopsy showed unquestionable evidence of fairly diffuse renal injury. According to this standard, none of the dogs used in this study could be considered as definitely nephropathic.

11 Lazarus-Barlow, P. The Effect of Intravenous and Intramuscular Inoculations of Novasurol in Rabbits, *Lancet* **1** 127, 1928.

12 MacNider, W. deB. A Pathological and Physiological Study of the Naturally Nephropathic Kidney of the Dog, Rendered Acutely Nephropathic by Uranium or by an Anesthetic, *J. M. Research* **34** 199, 1916.

## SUMMARY

Five dogs were given merbaphen in amounts corresponding to doses used therapeutically in man at varying intervals for periods up to five months. When the fluid and chloride intake were carefully controlled, and a sufficient period was allowed between doses of the drug, a diuresis and an increase in the urine chlorides always occurred during the twenty-four hours following the injection of the drug. On the other hand, when they were not controlled, both diuresis and increase in chloride output were inconstant. There was no constant change in the blood chlorides. The specific gravity and phthalein excretion remained normal. Albumin appeared irregularly, particularly after large doses repeated at short intervals. Casts also appeared after toxic doses. When the kidneys were examined histologically, there was evidence of early degeneration from three to nine days after the final doses of the drug. Some chronic change was present. This could not be attributed to merbaphen and was considered spontaneous. The kidney of one dog dying five days after a single lethal dose showed widespread tubular necrosis similar to that observed in the kidney of the rabbit and to that shown by various writers to be produced by toxic doses of other mercury compounds in common use.

## CONCLUSIONS

1 If the fluid intake is limited and the chloride intake is constant, diuresis with increase in the relative and total urine chloride always occurs following the injection of merbaphen. There is no constant change in the blood chlorides.

2 Repeated doses of merbaphen corresponding in amount to doses used therapeutically in man given over a period of five months produced no functional change in the kidney of the dog as evidenced by blood urea or nonprotein nitrogen, specific gravity, or phthalein excretion.

3 The kidneys of animals given repeated doses showed evidence of slight degeneration when examined histologically from three to nine days following the final dose. This was more marked following the larger doses and disappeared if the drug was discontinued.

4 In toxic doses the action of merbaphen on the renal parenchyma of the dog is similar to its action on the kidney of the rabbit and to the action of other mercury compounds in common use.

# SECRETION OF BILE IN RESPONSE TO RECTAL INSTILLATIONS<sup>\*</sup>

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Various studies in connection with the physiology of the secretion of bile have clearly shown that bile is being secreted constantly. The passage of bile into the intestines, however, occurs at intervals, for the liver, unlike every other gland except the kidney, has in connection with it a reservoir, the gallbladder, in which the bile accumulates and from which it is only expelled periodically.

One must, therefore, clearly understand and distinguish the bile-secreting from the bile-expelling mechanism. Heretofore, investigators attempting to study these two phases of secretion and expulsion have limited themselves to the response obtained after oral administration of different foods and chemicals. With the aid of the dye method, which visualizes the gallbladder, one is able to demonstrate the rate of filling and emptying of this reservoir following the intake of various foods and drugs. It is difficult to tell, however, whether the flow of bile thus obtained is simply a result of the secretion from the liver alone or whether it is associated with the emptying of the gallbladder, naturally, both factors may play a rôle.

Of the direct influence of nerves either on the secretion of bile or its expulsion, we have little definite knowledge. It is true that the secretion of bile or its expulsion may be distinctly affected by the section and stimulation of nerves which control the blood supply to the stomach, intestines and spleen, for the quantity of blood passing through these organs and the rate of secretion are diminished when the blood supply is greatly lessened. In this way, stimulation of the medulla oblongata, the spinal cord or the splanchnic nerves stops or slows the secretion of the bile by constricting the abdominal vessels, and the same effect can be reflexly produced by the excitation of afferent nerves.

Just what effect the instillation of various solutions high up in the lower bowel would have on the secretion and expulsion of bile was a question which presented itself during investigations in connection with another problem. In every instance we noted that shortly after the intro-

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<sup>\*</sup> Submitted for publication, March 1, 1929

duction of different solutions high up into the rectum, a flow of bile was obtained from the duodenal tube. This occurred within fifteen minutes after the rectal instillation and lasted from thirty to forty-five minutes. The bile was always light yellow at the onset and occasionally became darker as the drainage continued. Our next object was to determine whether this flow of bile was actually initiated by the instillation of these various liquids, and if so, what was the source of the bile? Did it come from the gallbladder or from the liver? Was it a phenomenon of liver secretion or of contraction of the gallbladder or of both?

A group of patients apparently free from disease was selected for investigation. Each patient was given a cleansing high enema at night, and after that the duodenal tube was passed. The next morning the proper position of the duodenal tube was ascertained, and aspiration was attempted to determine whether there was a spontaneous flow of bile through the tube. A large size rectal tube was then introduced as high up into the bowels as possible without causing the patient too much discomfort, usually about 12 inches (30.4 cm). One hundred fifty cubic centimeters of one of various solutions was next injected through the tube. The tube was then clamped at the end and left in place. At short intervals thereafter, aspiration of the duodenal tube was practiced, and the time of onset and cessation of the flow of bile was determined. In some cases the flow of bile started without aspiration. Chemical examinations of the blood and white blood cell counts and differential counts were made at varying intervals during the drainage of the bile.

The solutions employed for the instillations were (1) physiologic solution of sodium chloride, (2) indigo carmine (40 cc, 4 per cent), (3) dextrose (100 Gm), (4) phenolphthalein (2 cc standard alkaline solution to 150 cc physiologic solution of sodium chloride), (5) methylene blue (methylethionine chloride, U S P) (2 cc 5 per cent solution to 150 cc distilled water), (6) peptonized milk (150 cc)

#### REPORT OF CASES

GROUP 1 CASE 1—A man, aged 53, was admitted to the hospital with a diagnosis of chronic arthritis. On the evening of Feb. 12, 1928, the duodenal tube was passed, and a high cleansing enema was given. On February 13, 150 cc of phenolphthalein solution was injected through the rectal tube at 8.50 a. m., and a flow of bile was noted at 9 a. m., which continued until 9.45 a. m. A specimen of urine collected at 10 a. m. showed the presence of phenolphthalein. The two hour urinary excretion of phenolphthalein, following the rectal injection, was 11 per cent. No kidney lesion was present. On February 15, the procedure was repeated, but this time physiologic solution of sodium chloride was introduced at 9.10 a. m. At 9.21 a. m. a flow of bile was obtained, which continued until 9.45 a. m.

CASE 2—A man, aged 27, was admitted to the hospital with a diagnosis of malnutrition. On Feb. 18, 1928, 150 cc of peptonized milk was instilled into the rectum at 9.12 a. m. At 9.19 a. m., a flow of bile was obtained from the duodenal tube, it was extremely profuse and continued until 10.20 a. m. On February 22,

this procedure was repeated and 150 cc of a solution of phenolphthalein was introduced through the rectal tube at 8 55 a m. The flow of bile commenced at 9 01 a m and continued until 9 35 a m. At 10 15 a m a specimen of urine showed the presence of phenolphthalein. The total amount of phenolphthalein recovered in the urine at the end of two hours was 18 per cent. The subsequent functional tests of the kidney in this patient showed a normal excretion of phenolsulphonphthalein and failed to reveal any kidney insufficiency.

CASE 3—F B, a man, aged 46, was admitted to the hospital for observation, but no pathologic condition was discovered.

On Feb 24, 1928, 150 cc of physiologic solution of sodium chloride was injected through the rectal tube at 9 05 a m. A flow of bile was obtained from the duodenal tube at 9 12 a m, and it continued until 9 45 a m. On February 26, this procedure was repeated, peptonized milk being used. The milk was injected through the rectal tube at 9 12 a m, and a flow of bile was obtained at 9 17 a m, this continued until 9 54 a m.

CASE 4—E M, a man, aged 21, who was convalescing from a lobar pneumonia, was admitted to the hospital for observation.

On March 6, 1928, 150 cc of physiologic solution of sodium chloride was instilled into the rectum at 9 15 a m. At 9 18 a m, a flow of bile was obtained which was profuse and continued until 10 a m. On March 8, at 8 45 a m, this procedure was repeated, 150 cc of an indigo carmine solution being used. A flow of bile started at 8 53 a m and continued until 9 15 a m. On March 9, we attempted to see what effect simple inflation of the bowel with air would have on the flow of bile. At 9 05 a m, the lower bowel was distended to a moderate degree. No bile was obtained from the duodenal tube in spite of repeated aspirations for a period of one hour.

CASE 5—J L, a man, aged 45, was admitted with a diagnosis of ulcer of the stomach.

On March 11, 1928, 150 cc of physiologic solution of sodium chloride was introduced into the rectum at 8 45 a m. At 8 48 a m, a flow of bile began spontaneously from the duodenal tube and continued until 9 20 a m.

CASE 6—S G, a man, aged 37, was admitted to the hospital with a diagnosis of gastric ulcer.

On March 12, 1928, the duodenal tube was passed at 9 p m. On March 13, at 9 a m, 150 cc of peptonized milk was injected through the rectal tube. At 9 12 a m, bile began to flow and continued to flow until 10 a m.

The white blood cell count and differential count and the results of chemical examination of the blood in this case are recorded in the accompanying table.

CASE 7—C P, a man, aged 22, was admitted to the hospital for observation, but no pathologic process was discovered.

On March 26, 1928, 150 cc of a solution of methylene blue was injected into the rectum at 9 05 a m. At 9 17 a m, bile started to flow from the duodenal tube and continued until 9 55 a m. Methylene blue made its appearance in the urine at 10 30 a m.

CASE 8—J F, a man, aged 67, was admitted to the hospital with a diagnosis of mild diabetes.

On April 2, 1928, 150 Gm of dextrose was given per rectum at 9 20 a m. At 9 27 a m, bile began to flow from the duodenal tube and continued to do so until 10 15 a m. The blood sugar determination made at 9 10 a m just before the instillation, showed 180 mg, at 10 10 a m, it was 192 mg, at 12 15 p m, 200 mg.

Thus it is noted from this group of cases that flow of bile was stimulated by simple instillation of various fluids into the rectum

The results obtained in all of the cases are recorded in the accompanying table

After these experiments were completed, a second group of apparently normal persons was selected for study in order to establish whether the flow of bile came from the liver or from the gallbladder and

*A Review of Eight Cases in Group 1, Showing the Effect of Rectal Injections on the Flow of Bile*

Case	Date	Solution Used for Rectal Injection	Time	Time of Appearance of Bile from Duodenal Tube	Time of Cessation of Bile Flow	Remarks
1	2/13/28	150 cc phenolphthalein	8 50 a m	9 00 a m	9 40 a m	At 10 a m phenolphthalein was detected in urine
	2/15/28	150 cc physiologic solution of sodium chloride	9 10 a m	9 21 a m	9 45 a m	
2	2/18/28	150 cc peptonized milk	9 12 a m	9 19 a m	10 20 a m	At 10 15 a m phenolphthalein was detected in urine
	2/22/28	150 cc phenolphthalein	8 55 a m	9 01 a m	9 35 a m	
3	2/24/28	150 cc physiologic solution of sodium chloride	9 05 a m	9 12 a m	9 45 a m	
	2/26/28	150 cc peptonized milk	9 12 a m	9 17 a m	9 54 a m	
4	3/ 6/28	150 cc physiologic solution of sodium chloride	9 15 a m	9 18 a m	10 00 a m	
	3/ 8/28	150 cc indigo carmine	8 45 a m	8 58 a m	9 15 a m	At 10 a m indigo carmine appeared in urine
	3/ 9/28	Inflation of air into lower bowel	9 05 a m	None appeared as late as 1 hr thereafter		
5	3/11/28	150 cc physiologic solution of sodium chloride	8 45 a m	8 48 a m	9 20 a m	
6	3/13/28	150 cc peptonized milk	9 00 a m	9 12 a m	10 00 a m	
7	3/26/28	150 cc methylene blue	9 05 a m	9 17 a m	9 35 a m	At 10 30 a m methylene blue made its appearance in urine
8	4/ 2/28	150 Gm dextrose	9 20 a m	9 27 a m	10 15 a m	Blood sugar determination 9 10 a m, 180 mg 10 10 a m, 192 mg 12 15 p m, 200 mg

whether the mechanism was one of secretion or expulsion. To do this we employed the dye method of visualization of the gallbladder. The sodium salt of tetraiodophenolphthalein was given to the patient in capsule form at the time of passing the duodenal tube (i.e., the night before), and x-ray plates were made the next day at twelve and sixteen hour intervals after ingestion of the dye. Directly after the sixteen hour plates were taken, one of the various aforementioned solutions was instilled into the rectum and the time of flow of bile and its duration were

recorded. One hour after the rectal instillation, when the flow of bile had already ceased (which was seventeen hours after the administration of the dye capsules), another plate of the gallbladder was taken, and this was repeated at the eighteenth hour. At the nineteenth hour the usual fatty meal was given, and at the twentieth and thirty-sixth hours, plates were again made of the region of the gallbladder.

GROUP 2. CASE 1—F. X., a man, aged 65, was admitted to the hospital for observation of the condition of the gallbladder.

On the evening of March 13, 1928, the patient was given a cleansing enema, and then tetraiodophenolphthalein in capsules was administered by the oral method. The duodenal tube was passed. The following morning, at the end of the twelve hour period, x-ray plates revealed the gallbladder fairly well filled out with the dye. At the sixteen hour the x-ray picture showed the shadow to be practically of the same size but markedly increased in intensity.

The patient was then given 150 cc. of physiologic solution of sodium chloride per rectum, and within ten minutes a flow of bile was obtained from the duodenal tube. This steady drainage continued for thirty-five minutes. At the seventeenth, eighteenth and nineteenth hour periods, which corresponded to ten minutes and two hours after the rectal injection of the physiologic solution of sodium chloride, with its subsequent drainage of bile, the x-ray picture showed no reduction in the size of the gallbladder, but some intensification of the shadow. The duodenal tube was then removed, and the patient was given a fatty meal. Roentgen examination one hour after this food intake showed the gallbladder had emptied of the dye (fig.).

CASE 2—P. D., a man, aged 66, was admitted to the hospital on account of varicose veins of the lower part of the left leg.

On the evening of March 23, 1928, the patient received the usual preparations, as in case 1. Twelve hours after the intake of the dye, no distinct shadow was visible. At the sixteen hour, the shadow of the gallbladder could be fairly well outlined and appeared to be regular. The patient was then given a rectal injection of 150 cc. of peptonized milk, with the same result as regards the flow of bile from the duodenal tube as had been obtained in the previous cases.

Roentgen examinations were made one and two hours after the rectal injection. There was a marked concentration of the dye in the gallbladder, but no evidence of emptying. The patient was then given a meal and reexamined one hour later. The gallbladder was found markedly reduced in size. At the thirty-sixth hour, the shadow had entirely disappeared. Subsequent examination revealed no evidence of pathologic changes in the gallbladder.

CASE 3—W. K., a boy, aged 15, was admitted to the hospital with a diagnosis of chronic nephritis.

On April 1, 1928, the procedure mentioned in the preceding two cases was repeated. X-ray plates of the gallbladder taken after the injection of the peptonized milk into the rectum showed no emptying of the gallbladder in spite of the fact that bile was obtained through the duodenal tube.

CASE 4—L. C., a man, aged 28, was admitted to the hospital for observation.

On April 4, 1928, at the twelve hour period after the intake of the dye capsules, the gallbladder was not visible. At the sixteen-hour period, the shadow of the gallbladder was present. One hour after the injection of 150 cc. of peptonized milk into the rectum the shadow of the gallbladder had not decreased in size.



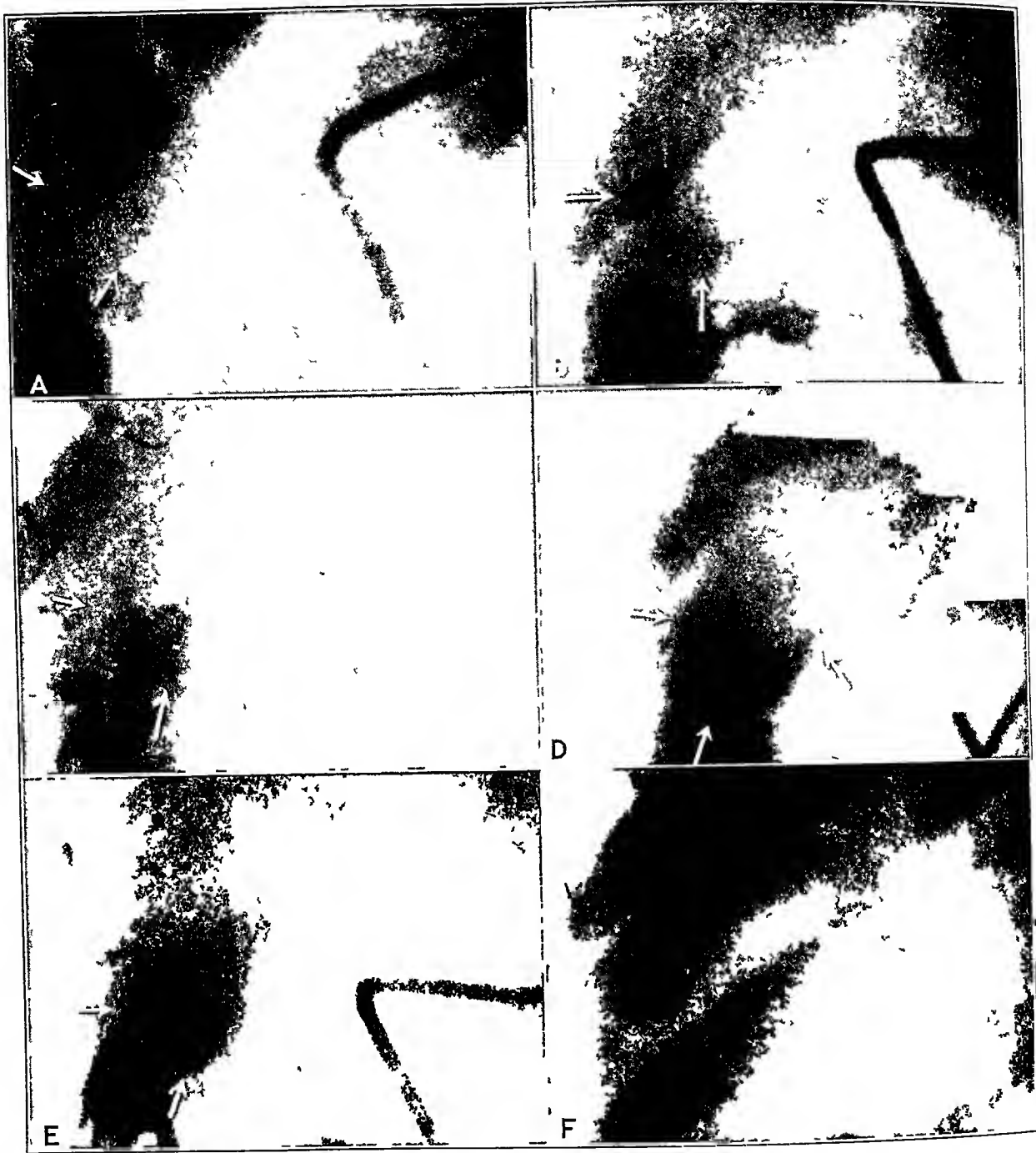


Fig 1—*A*, a roentgenogram, showing the dye method of visualization of the gallbladder, taken twelve hours after the administration of tetraiodophenolphthalein by capsules *B* shows the extent of the shadow sixteen hours after the administration of capsules of tetraiodophenolphthalein, *C*, the extent of the shadow ten minutes after the administration of a physiologic solution of sodium chloride per rectum, *D*, the extent of the shadow eighteen hours after the administration of capsules of tetraiodophenolphthalein, and one hour after injection of a physiologic solution of sodium chloride by rectum, *E*, the extent of the shadow nineteen hours after the administration of the capsules and two hours after injection of a physiologic solution of sodium chloride by rectum, and *F*, the extent of the shadow twenty hours after the administration of capsules and one hour after eating

but had become more intensified. At the two hour period after the injection, the shadow did not show up well because the patient breathed.

CASE 5—E. W., a man, aged 24, was admitted to the hospital for observation but no pathologic process was found.

On April 15, 1928, twelve hours after the dye had been taken by mouth, a definite shadow of the gallbladder was seen. Sixteen hours later, the shadow of the gallbladder was slightly contracted. One hour later, 150 cc of physiologic solution of sodium chloride was injected into the rectum, and shortly thereafter a flow of bile was obtained from the duodenal tube.

At the eighteenth hour, or one hour after injection of fluid into the rectum, the shadow of the gallbladder was more intensified and slightly larger in size. At the nineteenth hour, or two hours after the injection of physiologic solution of sodium chloride, the shadow of the gallbladder was still intense and remained about the same size. The patient was then given the fatty meal by mouth, and one hour after eating, which corresponded to the twenty-hour period after the intake of the dye capsules, the gallbladder appeared contracted and half the size. Thirty-six hours after the patient had taken the capsules no shadow of the gallbladder could be made out.<sup>1</sup>

#### COMMENT

In former years, irrigation of the colon was an established treatment for various types of jaundice. This paper offers the first proved experimental demonstration of the possible efficacy of this form of therapy.

In each of eight cases it was uniformly noted that within a period varying from three to twelve minutes after the instillation of various solutions high into the rectum, a flow of bile was obtained from the duodenal tube. This flow would continue for a period varying from eighteen to even as long as sixty-one minutes without any interruption. In three of the patients the rectal instillations were repeated once and in one of them twice. The solutions employed for instillation were, physiologic solution of sodium chloride, indigo carmine, peptonized milk, methylene blue, dextrose and phenolphthalein. This variety certainly precludes the possibility of any specificity in the response on the part of the liver. In one instance, case 4 (group 1) air was used to inflate the lower bowel, but no flow of bile was obtained as a result of this procedure, although the response had been obtained twice before in this patient after the use of physiologic solution of sodium chloride and a solution of indigo carmine. This fact would speak against a mechanical or nervous stimulation resulting from the mere filling of the rectum as being a cause for the secretion of bile. In the cases in which indigo carmine, methylene blue and phenolphthalein were employed, it was proved that these solutions were actually absorbed from the lower bowel, as they were detected in the urine at varying intervals after the rectal instillations. Similarly, in case 8 (group 1) a diabetic patient on whom dextrose solution was

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<sup>1</sup> Only the x-ray plates in connection with case 1 are reproduced. The x-ray pictures in association with the other cases are just as striking, but were not published on account of lack of space.

employed, the blood sugar determinations showed a progressive rise at the one and three hour periods

These facts thus reveal that the introduction of various solutions into the lower bowel causes a definite flow of bile into the intestines. The mechanism whereby this is brought about is either a direct stimulation of the cells of the liver from the absorption of the instilled fluids into the portal system or a reflex nervous phenomenon. The former is the more probable explanation.

Further study will be undertaken to prove this point by the use of agents which are known to have a direct stimulating effect on the liver cells and by noting the quantity of bile obtained in comparison with the agents which are not especially cholagogue in action. This method of bile drainage may prove of therapeutic importance in those cases in which bile drainage by means of Lyon's method is impossible or inadvisable.

Another group of cases was studied for the purpose of determining whether such flow of bile was the result of stimulation of the bile-secreting or bile-expelling organs. Conclusive proof is offered by means of the x-ray picture (fig.). Twelve hours after the ingestion of the tetraiodophenolphthalein, a fairly large and distinct shadow of the gallbladder is present. At the sixteen-hour period the shadow is slightly larger and more intense. At the seventeenth hour, the physiologic solution of sodium chloride is introduced rectally, and ten minutes later, when the bile commences to flow, another plate taken shows the gallbladder about the same size as that previously noted but slightly more intense. The physiologic solution of sodium chloride is given at approximately the time when the usual fatty meal is employed to stimulate the contractions of the gallbladder. After a profuse flow of bile is obtained, other plates, taken at the eighteenth hour or one hour after the introduction of the physiologic solution of sodium chloride per rectum, and at the nineteenth hour, or two hours following the rectal instillations, reveal the gallbladder to be practically the same size as at the sixteenth hour and the shadow slightly more intensified. On the other hand, the usual fatty meal then administered brings about contraction of the gallbladder so that at the twentieth hour the shadow of the gallbladder is practically absent.

#### CONCLUSION

The introduction of various solutions into the upper rectum produces a drainage of the bile into the duodenum. This flow comes directly from the liver without contraction of the gallbladder.

## Book Reviews

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MUSCLE FUNCTION By WILHELMINE G WRIGHT Cloth Price, \$3.50  
Pp 188, with 26 illustrations New York Paul B Hoeber

Wright's "Muscle Function" fills a space long left vacant in orthopedic literature, that of a practical discourse on the function of muscles presented in a readily available form as an aid to the surgeon and the physical therapist. Here is a work at once practical and exact, grown out of the constant observation of a skilled physiotherapist at one of the best infantile paralysis clinics in the country. At this clinic the author was guided in her work by the late Dr. Robert W. Lovett, to whom the treatise is respectfully dedicated. The foreword is by I. Playfair McMurrich, who points out that the method utilized in determining the exact function of the individual muscles and groups is superior to the anatomic and electrical methods, since, as Miss Wright emphasizes, it tells us not "what a muscle may do but what a muscle does do." Miss Wright has applied the physiologic method to patients whose paralyzes make the confusing group and influences of antagonistic action less of a problem. By the elimination of superficial muscles the interpretation of the action of the deep-seated ones is made less difficult.

The work is divided into seven chapters: (1) general principles of muscle action, (2 to 6) movements of the limbs, head, neck, spine and respiration, and (7) a list of muscles giving the action in which each takes part. The illustrations are chiefly diagrammatic with a few taken from instructive cases seen at Dr. Lovett's clinic. They are too few in number but are well chosen in general. The final chapter makes an excellent reference for those who require an accurate and practical knowledge of the action of individual muscles and groups. Miss Wright's efforts are well worth while and should find a grateful group of enthusiasts.

TUMORES PRIMITIVOS DE LA PLEURA By JOSE W TOBIAS Buenos Aires  
Libreria El Ateneo, 1928

This is a scholarly monograph of 479 pages on primary tumors of the pleura. Most of it is taken up with a discussion of the so-called endotheliomas of the pleura. The term includes perhaps many tumors which have their origin in the underlying epithelial tissue of the lung, but the terminology is so confusing that it is just as well to group these tumors under one head as the clinical syndrome is rather clearcut.

The author has made intensive pathologic studies on several such cases, and it seems likely that they really are endotheliomas. These are reported in detail and are lavishly illustrated with both gross and microscopic preparations, many in color.

Every feature of the disease is clearly outlined, and the literature on the subject is reviewed thoroughly. Illustrative cases are often given. The difficulty in diagnosis is emphasized, and several chapters are devoted to the signs, symptoms and diagnosis. It is unfortunate that the roentgenologic evidences are not more carefully analyzed. The prognosis is of course hopeless and the treatment purely symptomatic.

The remainder of the work is devoted to a less detailed discussion of the rarer sarcoma, the benign growths, granulomas and cysts.

THE TREATMENT OF VARICOSE VEINS BY INTRAVENOUS INJECTIONS By  
J P L McLATCHIE Price, \$1.60 New York The Macmillan Company,  
1929

This is a small monograph of fifty pages. It consists mainly of detailed descriptions of the preparation of the solutions used for injections and of the technique of

injections Sodium salicylate is recommended most highly and quinine is the next choice in cases in which the pain from the former is too great. Emphasis is placed on the fact that any obliterative or coagulant solution spilled in the tissues is liable to cause extensive sloughing.

While the work has value as a technical handbook, it does not even begin to answer the important question as to whether treatment by injection is the method of choice. The author assumes that it is, and states that there never has been an embolus from the injection of quinine, a statement which is open to grave doubt. The whole matter of emboli, sloughing, whether real cures are brought about and whether either the morbidity or the mortality is less than in open operation cannot be considered as settled until a detailed analysis of parallel series of cases is published showing the true facts of the case. Such a work is far more needed than the present publication.

AN INDEX OF SYMPTOMATOLOGY Edited by H. LETHEBY TIDY Price, \$12  
Pp 710 New York William Wood & Company, 1929

The book is intended to provide an account of the symptomatology of diseases. A clear and reasonably full description of the clinical manifestations of each disease is included, as are the usual and most important complications. No method of treatment is given. The contributors are all English and are men of wide reputation. Each description is signed. The fields of medicine, surgery, gynecology and various special subjects have been well covered. This book should be of great value to any one looking for a concise description of diseases and not caring to enter the fields of physiology or pathology as applied to them. It is well edited, and the purpose for which the book was written is amply fulfilled.

MODERN MEDICINE Its Theory and Practice in Original Contributions by American and Foreign Authors Edited by Sir William Osler, Bart, M.D., F.R.S. Third edition, thoroughly revised, reedited by Thomas McCrae, M.D., assisted by Elmer H. Funk, M.D. General Index Price, \$1 Philadelphia Lea & Febiger, 1928

This is a volume of 126 pages containing a complete index of Osler and McCrae's "Modern Medicine." The index is exhaustive and accurate. Bound separately in a handy volume it serves an excellent purpose as to convenience. Through it, all the subject matter of the six bulky volumes of this great work is made readily available.

## EDEMA IN CONGESTIVE HEART FAILURE EFFECTIVENESS OF DIURETICS AS A GUIDE TO PROGNOSIS

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During the past fifteen years many investigators have concerned themselves with the problem of edema. Physical, chemical and other factors have insufficiently explained the ultimate cause of the retention of abnormal amounts of fluid in the interstitial tissues and serous cavities of the body. The final solution of the problem rests on further knowledge of factors not yet sufficiently understood, such as capillary permeability, abnormal distribution of sodium chloride and colloids, and other factors possibly of lesser importance, such as changes in H-ion concentration and hormones. The vast literature on the subject of edema includes many factors which may play a part, but the pathogenesis of this condition can be fully understood only when further correlation between them is established.<sup>1</sup>

In spite of this lack of specific knowledge, definite advance has been made in recent years in regard to methods of treatment. This has frequently been arrived at empirically, and neither the nature of the action of some diuretics nor the type of edema in which they are most useful has been determined. This paper is concerned with a study of certain diuretic substances which have achieved prominence, and particularly with their ability to remove fluid in cases of congestive heart failure, when rest and full digitalis medication have proved ineffective. Many drugs have been used as diuretic substances when cardiac edema persisted in spite of full digitalization. On reviewing the literature, however, one gains the impression that those found to be most useful are urea, synthetic theophylline and preparations of mercury in combination with the acid-forming salts, ammonium chloride and ammonium nitrate.

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\* Submitted for publication, April 20, 1929.

\* From the Third Medical Division of Bellevue Hospital (New York University).

1. Loeb, L. Edema, Baltimore, Williams & Wilkins Company, 1923.

Urea was first introduced as a diuretic by Friedrich,<sup>2</sup> in 1892, and was then used by Feilchenfeld,<sup>3</sup> in 1918, and Strauss,<sup>4</sup> in 1921, all of whom reported favorable results. Crawford and McIntosh<sup>5</sup> studied urea as a diuretic in edema due to heart failure. They studied eight patients, seven of whom showed clinical improvement with marked diuresis. They stated their belief that urea was rapidly absorbed, quickly raising the blood urea, and being a nonthreshold substance, was rapidly excreted, carrying water to the kidney. The beginning effect of urea was seen from forty-eight to seventy-two hours after administration of the drug. Keith and Whelan's<sup>6</sup> objection to urea was that as a salt it carried only water to the kidney, leaving the retained sodium chloride behind in the tissues, and for this reason was a less efficient diuretic than those which remove both water and retained sodium chloride.

Calcium gained some prominence as a diuretic in 1918, as a result of studies made by Schultz<sup>7</sup> in edema due to war nephritis. Many theories have been advanced to explain its action. However, the fact that the chloride of calcium is said to be more effective than the lactate, suggests that the active agent in the preparation may be the anion, in which respect the salt of calcium acts as any other acid-forming salt. Bowler and Walters,<sup>8</sup> in some experimental work with calcium, showed that in lethal doses it produced no anatomic or pathologic change in the kidneys of animals. Rockwood and Barrier<sup>9</sup> used calcium clinically in treatment for edema. They agreed with Schultz that it was of value in edema due to nephritis, nephrosis, cirrhosis of the liver and pleural effusion, but was of no value in edema associated with heart failure.

Of the xanthine diuretics, synthetic theophylline has proved of value. Theophylline has long been considered to act directly on the epithelium

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2 Friedrich, W. (Ueber die harntreibende Eigenschaft des Uream) As ureum hugyhajto tulajdonsargarol. Kozlemeny u budapesti Magy kir tud Egyetem gyogyozertani intezelebal, Magy orv Arch **1** 400, 1892.

3 Feilchenfeld, J. Ueber Harnstoff als Diureticum, Therap d Gegenw **59** 273, 1918.

4 Strauss, H. Ueber Harnstoff als Diureticum, Berl klin Wchnschr **58** 375, 1921.

5 Crawford, J. H., and McIntosh, J. F. The Use of Urea as a Diuretic in Advanced Heart Failure, Arch Int Med **36** 530 (Oct) 1925.

6 Keith, N., and Whelan, M. A Study of the Action of Ammonium Chlorid and Organic Mercury Compounds, J Clin Investigation **3** 149 (Oct) 1926.

7 Schultz, E. Klinische Beobachtungen uber Nierenentzundung bei Kriegsteilnehmern, Ztschr f klin Med **86** 111, 1918.

8 Bowler, J., and Walters, W. The Effect of the Intravenous Injection of Calcium Chloride on the Kidney, J A M A **83** 1232 (Oct 18) 1924.

9 Rockwood, R., and Barrier, C. W. Calcium Treatment for Edema, Arch Int Med **33** 643 (May) 1924.

of the kidneys. Investigations by Fleisher and Loeb,<sup>10</sup> however, seemed to indicate that the action of the caffeine diuretics was not directly on the epithelium of the kidney but on the blood itself, calling forth some condition which started a movement of sodium chloride from the blood to the tissues. Cushny<sup>11</sup> expressed the opinion that the xanthines acted directly on the epithelium of the kidneys, causing increased filtration through the glomerular capsule and probably lessened reabsorption in the tubules. Cessation of diuresis after prolonged administration of the drug, he considered to be due to a further effect on the glomerular epithelium causing a diminution in its permeability. In its practical application, theophylline has proved to be a satisfactory diuretic.<sup>12</sup>

Most recent investigators<sup>13</sup> expressed the belief that the most effective agent at this time for relief from cardiac edema was compounds of mercury in combination with the acid-forming salts, ammonium chloride and ammonium nitrate. Merbaphen is a double salt of sodiumoxymercuriochlorphenoxy acetate with diethyl barbituric acid. It was introduced, in 1920, by Saxl and Heilig.<sup>14</sup> Its diuretic property was noted incident to its use as an antisypilitic in decompensated syphilitic disease of the heart. Merbaphen itself contains 33.9 per cent of mercury in a complex nonionizable combination. As a diuretic, however, it is employed in a 10 per cent solution.

Most of the earlier investigations were made in Germany,<sup>15</sup> with the exception of those by Neuhof<sup>16</sup> of New York who reported favorable results, in 1924, in a series of eight patients.

In those patients in whom merbaphen is effective, the diuresis begins from three to four hours after the injection and continues to a lesser degree during the following twenty-four hours.<sup>17</sup> The point of action of merbaphen has not yet been definitely determined.

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10 Fleisher, M. S., and Loeb, L. The Influence of Caffeine on Absorption from the Peritoneal Cavity and the Influence of Diuresis on Edema, *J. Exper. Med.* **12** 510, 1910.

11 Cushny, A. R. The Secretion of Urine, New York, Longmans, Green & Company, 1926.

12 Marvin, H. M. The Value of the Xanthine Diuretics in Congestive Heart Failure, *J. A. M. A.* **87** 2043 (Dec. 18) 1926.

13 Keith and Whelan (footnote 6). Crawford, J. H., and McIntosh, J. F. Observations on the Use of Novasurol in Edema Due to Heart Failure, *J. Clin. Investigation* **1** 333, 1925. Oerting, H. *Minnesota Med.* **8** 593 (Sept. 8) 1925. White, A. E. R., and Zacharin, David. *M. J. Australia* **1** 273 (Feb. 19) 1927.

14 Saxl, P., and Heilig, R. Ueber die diuretische Wirkung von Novasurol und anderen Quecksilberinjektionen, *Wien klin. Wchnschr.* **33** 943, 1920.

15 Biedermann, J. *Gyogvaszat*, no. 6, 1921. Eppinger, H. *Therap. d. Gegenw.*, March, 1921.

16 Neuhof, S. *Therap. Gaz.*, Jan. 15, 1924.

17 Keith and Whelan (footnote 6). Biedermann (footnote 15, first reference). Eppinger (footnote 15, second reference).



Jacobs and Keith<sup>18</sup> showed what they termed remarkable diuresis in three patients with heart failure and edema, in whom only the acid-forming salts were used. They assumed that the action was due to the anion, probably by changing the H-ion concentration of the tissues and the tissue fluids. This acidosis diuresis was previously noted by Haldane<sup>19</sup>.

Keith, Barrier and Whelan<sup>20</sup> had shown striking results with the combination of ammonium chloride and merbaphen. They repeated the study<sup>6</sup> and confirmed the previous good results with the combination. In those patients who reacted to the combination of diuretics the following facts were noteworthy: a shift of the acid base equilibrium to the acid side, and a fall in the plasma chloride to below the normal threshold of about 336 mg per hundred cubic centimeters during the height of the diuresis, with a slow rise to normal when the diuresis had ceased. This fall in plasma chloride had previously been noted by Crawford and McIntosh<sup>21</sup>. The action of merbaphen and ammonium chloride in combination as an effective diuretic would seem to be the ability of merbaphen to mobilize and cause the excretion of sodium chloride in a slightly acid medium<sup>6</sup>.

#### METHODS OF TREATMENT

During the past two and one-half years in this clinic diuretics have been administered to forty-six patients with heart failure and persistent edema, on eighty-five different occasions. A definite routine was followed in studying each case. The patients were put to bed and, unless there were some special indications, digitalis was withheld until the weight was stationary for about five days or until it was evident that rest alone would not cause further loss of weight from relief from edema. Digitalis was then given in a routine manner to the point of mild toxicity, after a rest of twenty-four or forty-eight hours when all signs of toxicity had disappeared, it was resumed in maintenance dosage. The intake of fluid was limited to about 1,200 cc in twenty-four hours and the diet was deficient in salt. The patient was weighed every morning and his daily urinary output was regularly measured. When it was apparent that there could be no further loss of weight from digitalis, which was usually from seven to ten days after complete digitalization, a diuretic was administered. Digitalis in maintenance dosage was continued throughout the period of administration of the diuretic.

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18 Jacobs, N. and Keith, N. The Use of Diuretics in Cardiac Edema, *M. Clin. North America* **10** 605 (Nov.) 1926.

19 Haldane, J. B. S. Experiments on the Regulation of the Blood's Alkalinity, *J. Physiol.* **55** 265 (Aug.) 1921.

20 Keith, N. M., Barrier, C. W., and Whelan, M. The Diuretic Action of Ammonium Chloride and Novasurol in Cases of Nephritis with Edema, *J. A. M. A.* **85** 799 (Sept. 12) 1925.

21 Crawford and McIntosh (footnote 13, second reference).

*Urea*—Urea was administered to four patients in doses of from 30 to 60 Gm a day. Special precautions were taken to give the drug well diluted and immediately after meals, in single and divided doses, but with no freedom from the gastric irritation. In each instance it induced vomiting and had to be discontinued before its diuretic effect could be determined. Crawford and McIntosh,<sup>5</sup> however, reported favorable results in seven of eight patients whom they studied.

*Calcium*—Calcium chloride and calcium lactate given in doses of from 60 to 180 grains (3.9 to 11.7 Gm) daily, both by mouth and intravenously, proved ineffective in six patients of the present series of patients with cardiac edema although the remarkable effect of this drug was noted in some cases of nephritic edema.

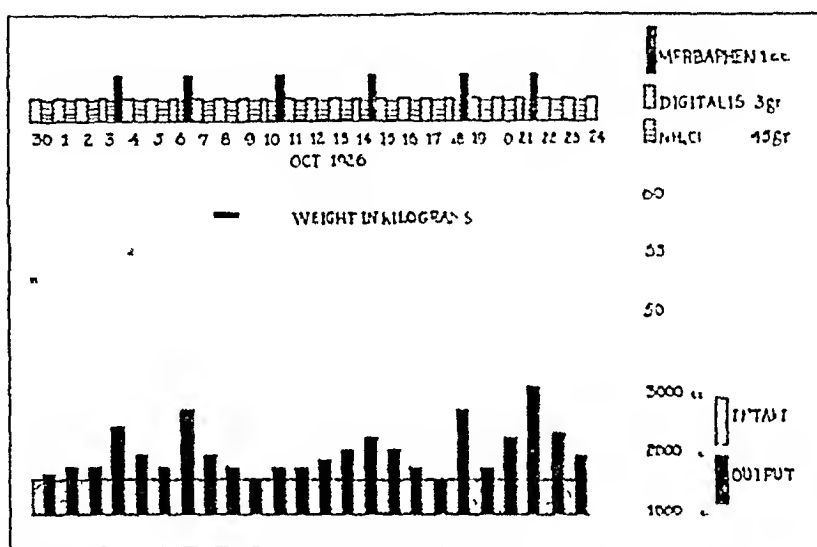


Chart 1—Effect of diuretics on a white man aged 48, with rheumatic disease of the heart. No loss of weight was noted after digitalization, and complete relief from edema was obtained. The patient remained free from edema for five months. (Complete chart is not shown.)

*Acid-Forming Salts*—Following the work of Jacobs and Keith<sup>18</sup> the acid-forming salt, ammonium chloride was administered to eight patients. In each case it failed to produce a diuretic effect. It was used in doses up to 120 grains (7.8 Gm) daily. Chart 3 shows one case in which doses of 60 grains (3.9 Gm) daily over a period of fifteen days did not induce diuresis. Keith and Whelan<sup>19</sup> reported definite diuresis in three patients with nephritic edema and the ascites of portal cirrhosis, to whom ammonium chloride was given. Gamble, Blackfan and Hamilton<sup>22</sup> reported the theoretical value of the acid-forming salts in edema, but they used only one case of nephritic edema and two patients

<sup>22</sup> Gamble, J. L., Blackfan, K. D., and Hamilton, B. A Study of the Diuretic Action of Acid Producing Salts, *J. Clin. Investigation* 1: 359 (April 20) 1925.

without edema. Since the present study was made on edema associated with cardiac failure, this may explain the difference in the results.

Occasionally a patient is encountered in whom ammonium chloride induces nausea and less frequently vomiting. In no instance was it necessary to discontinue the drug because of its gastric effect. This was overcome in one patient by giving the ammonium chloride by rectum. In other patients the ammonium chloride was given well diluted and immediately after meals with the prompt disappearance of gastric symptoms. In others it was necessary to use from four to twelve capsules to make up the desired daily dose. Instances of acidosis have been noted after

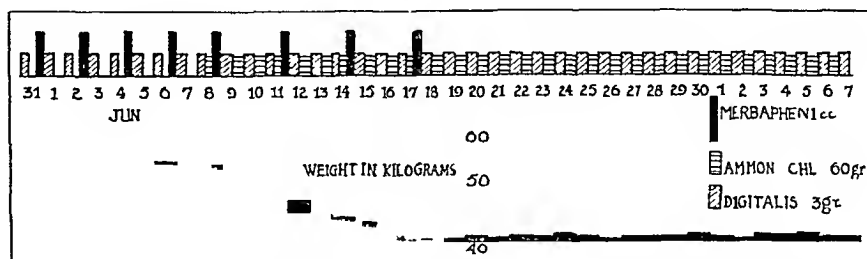


Chart 2—Effect of diuretics on a white woman, aged 38, with active rheumatic disease of the heart. Marked diuresis was noted only after the addition of ammonium chloride. (The complete chart indicating digitalization is not shown.) Immediate clinical improvement was marked, but the patient died of progressive heart failure five months later.

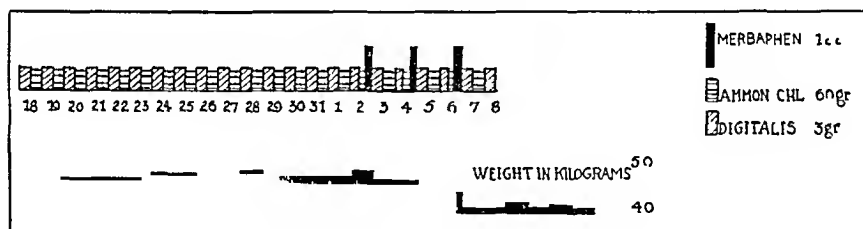


Chart 3—Further data on the same patient as in chart 2. Note the ineffectiveness of ammonium chloride when given alone, and the rapid loss of weight when merbaphen is added. (Control and digitalis observations are omitted.)

prolonged administration of the drug<sup>19</sup>. This was not observed clinically by me, although the dosage given was considered adequate.

*Merbaphen*—Merbaphen was administered alone to sixteen patients, with relief from edema in only five. The dose given was 1 cc intramuscularly every fourth day, when this dosage was ineffective the drug was given every other day. No case in which a result was not obtained on the lower dosage was affected by increasing the frequency of the injection. If no diuresis was noted after the third or fourth injection, merbaphen was considered ineffective and was discontinued. As has been noted,<sup>23</sup> when diuresis occurred it usually began three or four hours

<sup>23</sup> Keith and Whelan (footnote 6). Biedermann (footnote 15, first reference). Eppinger (footnote 15, second reference).

after the injection and continued for the next twenty-four hours. Occasionally, there was some persistence of the diuresis in the following twenty-four hours. In thirty-one instances in which it was given, either alone or in combination with ammonium chloride, a bloody stool was noted in only one, and this after two intramuscular injections of 1 cc four days apart. In four other instances soreness of the gums called for cessation of the treatment. In two patients the drug was improperly administered by the nurse who gave it subcutaneously rather than intramuscularly. This faulty technic resulted in a local slough in both cases.

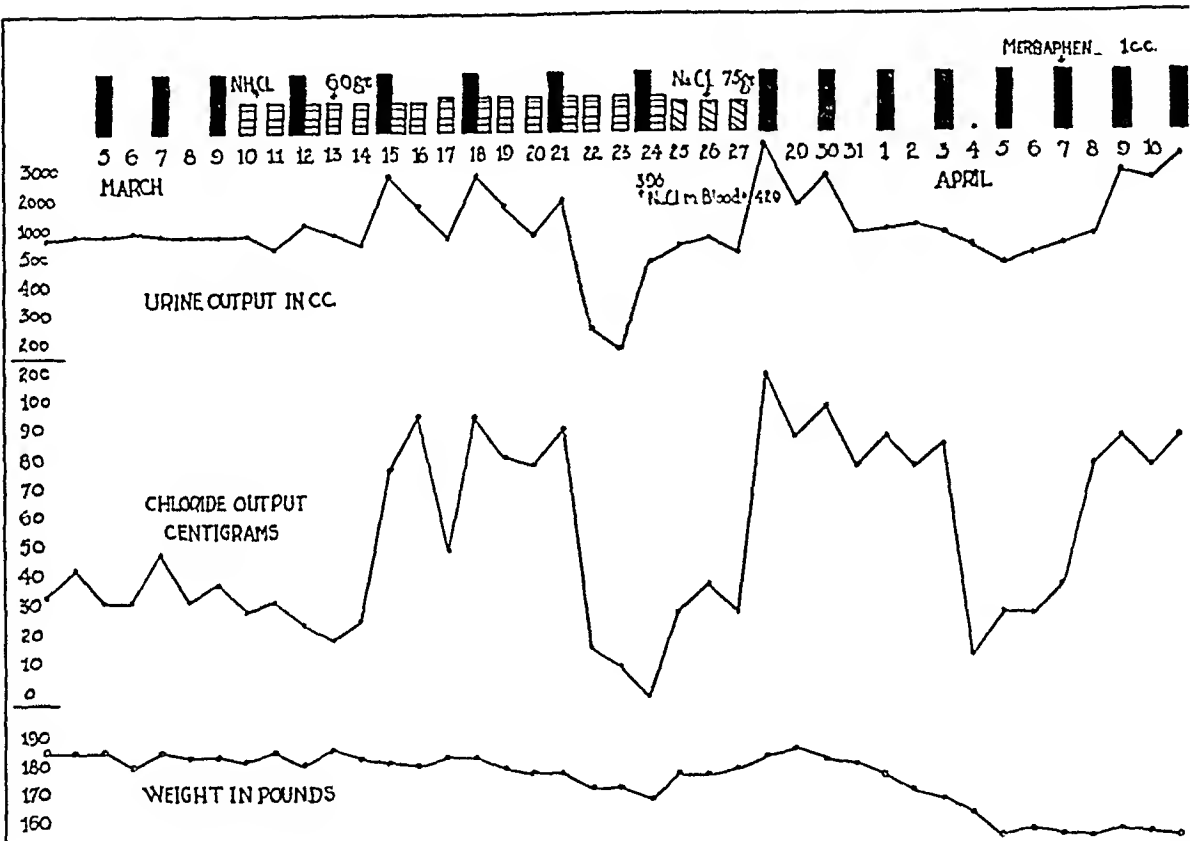


Chart 4—Effect of diuretics on a white man, aged 37, with active rheumatic disease of the heart. (The complete chart is not shown.) Observe the stimulating effect of sodium chloride on diuresis. The excretion of urine and chloride was determined daily, it is drawn to a semilogarithmic scale. The weight was used as the guide to the effect.

*Merbaphen and Ammonium Chloride Combined*—In fifteen instances in which ammonium chloride alone or merbaphen alone was ineffective, the combination of both produced quick and dramatic effect in fourteen patients or about 93 per cent. The effectiveness of this combination is clearly shown in charts 1, 2, 3 and 5. In the patients in the latter three charts, the single medication was apparently insufficient to initiate diuresis.

*Theophylline*—Synthetic theophylline was administered thirty-two different times. It was effective in entirely removing the edematous fluid in twenty instances or 62.5 per cent. It was given in doses of from 9 to 30 grains (0.58 to 1.95 Gm.) daily in capsule. The dosage was increased only when the smaller amount was ineffective. When the urinary output diminished, the theophylline was discontinued for about three days on the assumption that it was producing a direct inhibitory effect on the glomerular capsule.<sup>11</sup> In a few patients theophylline induced nausea and occasionally vomiting, even with smaller doses. In these patients it was discontinued and some other diuretic was used. This toxic effect, however, was not found to be the rule when the theophylline was given with meals and well diluted.

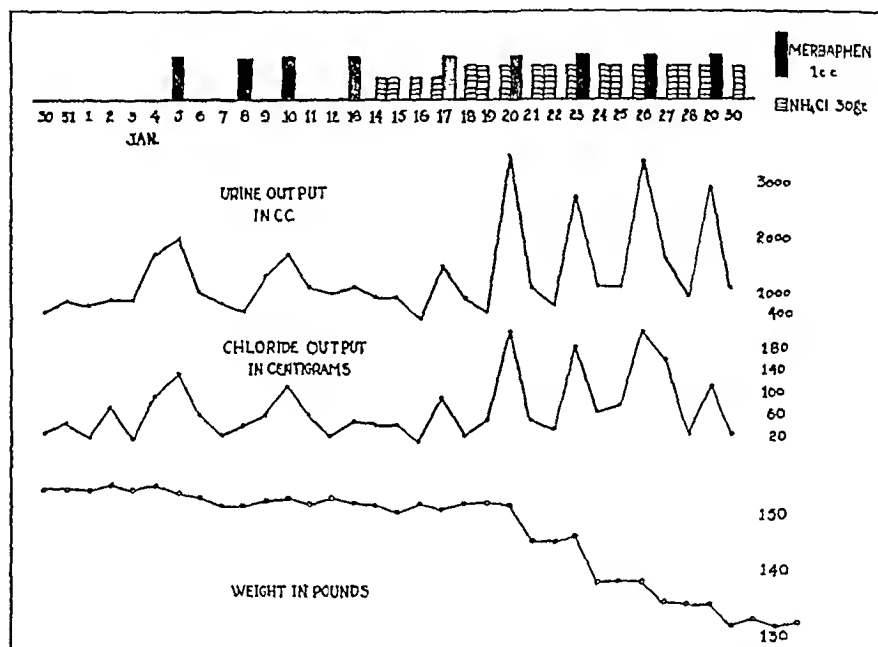


Chart 5—Effect of diuretics on a youth, aged 19, with active rheumatic disease of the heart. The urinary and chloride output is charted on a semilogarithmic scale. Note the apparent ineffectiveness of merbaphen when given alone and the need for persistence in the treatment for edema.

*Diuretin*—After using diuretin in doses of from 30 to 45 grains (1.95 to 2.92 Gm.) daily with no effect in four patients, it was discontinued because of the availability of more effective diuretics. This inadequate activity of diuretin as a diuretic had been noted by others.<sup>24</sup>

#### COMMENT

Because of the high percentage of effectiveness with merbaphen and ammonium chloride, in combination, it would seem that this is the

<sup>24</sup> Marvin (footnote 12) Taylor, Lester. Clinical Studies in Caffeine, Arch Int Med 14 769 (Dec) 1914.

diuretic of choice in the treatment for edema associated with heart failure. It should be used with caution where there is an associated nephritis, hypertension, exudate or hemorrhage in the retinas and even in the case of elderly persons, starting with injections of 0.5 cc at as great an interval as possible (one week at least) and watching carefully for the first signs of toxicity.

Relief from cardiac edema in certain patients is more or less simple, requiring only the exhibition of a known diuretic substance in a fixed scale of dosage. When this method fails to effect diuresis further measures are necessary. In two patients of the present series there was a cessation of the effect of merbaphen and ammonium chloride before complete relief from edema had been effected. It was thought that the blood chloride, as determined at that time, was below the kidney threshold and consequently no diuresis was possible. Accordingly, both patients were given sodium chloride. Five grams was given by mouth

*Comparative Action of Diuretics*

Diuretic	Number of Trials	Effective *	Not Effective	Reaction per Cent
Merbaphen and ammonium chloride	15	14	1	93.0
Theophylline	32	20	12	62.5
Merbaphen	16	5	11	31.0
Ammonium chloride	5	0	5	0
Urea	4	0	4	0
Calcium	6	0	6	0
Diuretin	4	0	4	0
Total	87	40	46	---

\* Complete relief from edema

on three successive days, raising the blood chloride in one patient from 246 to 445 mg, and in the other patient who responded, from 396 to 429 mg. Merbaphen alone given at this point produced quick and complete relief from edema.

These two cases raise the question of the relationship of the blood chloride level to the effectiveness of merbaphen as a diuretic. Chart 4 illustrates one of the cases in which sodium chloride appeared to add to the effectiveness of the diuretic. It is of interest, that while merbaphen alone was insufficient at the beginning, after the administration of the sodium chloride it produced a rapid diuresis without the aid of ammonium chloride. Keith and Whelan<sup>6</sup> likewise noted this cessation of diuresis when the plasma chloride content was below the normal threshold. In one case they administered ammonium chloride with satisfactory results, but when sodium chloride was administered the patient's weight increased and diuresis did not occur. The diuresis in the present cases, however, only followed the further administration of merbaphen, and the sodium chloride seemed clearly to augment its

effectiveness, whereas in Keith and Whelan's case a diuretic was not given following the sodium chloride

The accompanying table is arranged to show the comparative action of the diuretics. It gives the diuretics used, the number of trials of each and their effectiveness. They were effective in completely removing edematous fluid in thirty-nine instances and ineffective in forty-six

Marvin<sup>25</sup> found that in patients with congestive heart failure occurring with arteriosclerotic disease of the heart, the edema was more often relieved than the edema occurring with other etiologic types of disease of the heart. Chart 6 shows that this is not my experience. In rheumatic disease of the heart, 80 per cent reacted to diuretics while in arteriosclerotic disease of the heart, only 37 per cent reacted. The small

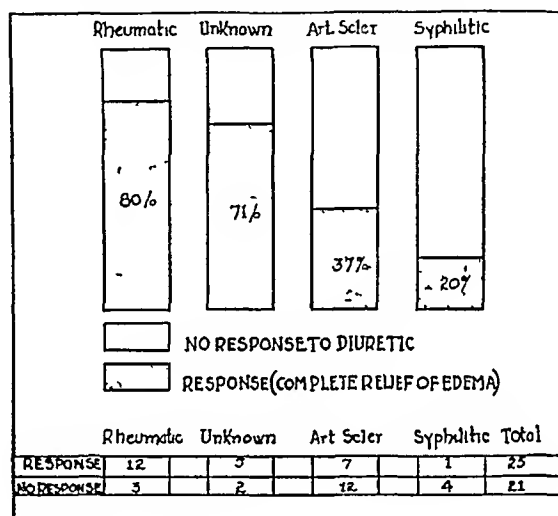


Chart 6—Response to a diuretic according to the etiologic type of disease of the heart

percentage (20 per cent) of reaction in the syphilitic group is interesting. In view of this observation it is difficult to accept Marvin's statement that "individuals with rheumatic heart disease seldom show satisfactory diuresis." Not only was the best percentage of reaction noted in the rheumatic group, but even the presence of persistent cardiac activity did not seem to hinder the effectiveness of the diuretic. This is shown in chart 7.

In the course of this study it seemed that there was a definite prognostic significance in the reaction or failure of reaction to a diuretic. Chart 7 shows an analysis of the patients to determine this fact. Of twenty-one patients who did not react to one or more diuretics, only six

<sup>25</sup> Marvin, H. M. Digitalis and Diuretics in Heart Failure with Regular Rhythm, with Especial Reference to the Importance of Etiologic Classification of Heart Disease, *J. Clin. Investigation* 3: 521 (Feb.) 1927.

left the hospital alive, all were in a precarious condition and left at their own request. On the other hand, of twenty-five patients who responded to diuretics, fifteen were able to leave the hospital in an improved state, even though some degree of heart failure persisted. This seems to indicate that reaction to a diuretic under the conditions of this study is a distinct guide to the immediate prognosis. A follow-up was made, in the Out-Patient Cardiac Clinic, in only six of the fifteen patients discharged as improved after complete relief from edema by means of a diuretic. While the total number is small it shows the tendency of most of these patients to decline rapidly into progressive heart failure and to die in a comparatively short time after discharge from the hospital. This is shown in chart 7.

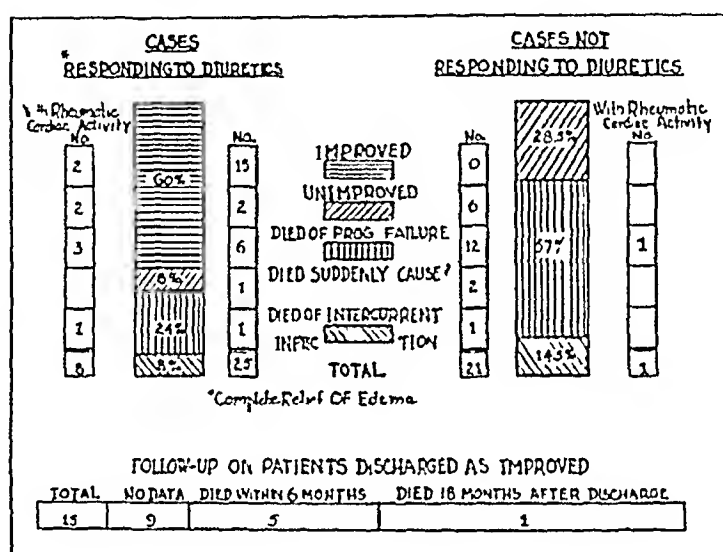


Chart 7—Relationship between the reaction to a diuretic and the immediate prognosis. Only one of the patients discharged as improved was alive at the end of the year.

A study of chart 7 shows that of forty-six patients with congestive heart failure who did not react to digitalis by diuresis (although the vagal effect was marked in most cases) twenty-eight died within six months, and seventeen were discharged from the hospital with varying degrees of congestive failure. One patient who reacted to a diuretic died of congestive failure eighteen months later.

While one may not wish to draw any conclusions concerning the value of the reaction to diuretics as a guide to immediate prognosis, this study indicates that in the entire group of patients who do not respond to digitalis by diuresis it is exceptional for life to exceed six months. Marvin's<sup>25</sup> figures in this regard are comparable to mine. There is no evidence from the present study or from the literature that relief from edema by means of a diuretic after digitalis has failed, does any more



than temporarily influence the prognosis. Since edema of this type is due directly or indirectly to a failing myocardium which does not respond to the best therapeutic measures at one's command, rest and digitalis, it is obvious that diuresis is only a palliative measure. While a favorable diuretic effect increases the expectancy of life in some patients for a short time, its greatest value lies in relief from one of the most distressing features of terminal heart disease, anasarca.

#### SUMMARY

Cardiac edema can be relieved by digitalis in most instances.

In those patients in whom digitalis is ineffective, diuresis may be produced frequently by other drugs.

Of the many diuretics at my disposal, theophylline and merbaphen, in combination with ammonium chloride, have been most useful.

In a series of forty-six patients with congestive heart failure in whom edema was not relieved by digitalis, diuretics were successful in twenty-five cases, or about 54 per cent.

The greatest incidence of reaction was noted in the rheumatic group.

A striking incidence of reaction was noted in the rheumatic group with persistent cardiac activity.

It may be that the cessation of diuretic effect before edema is completely relieved is due to a temporary depletion of blood chloride. This appears to be borne out by two patients in the present series.

The failure of reaction to adequate digitalization indicates a marked diminution of cardiac reserve. Even when the patients subsequently reacted to a diuretic by complete relief from edema, length of life exceeded six months in only one instance.

# BLOOD SUGAR REGULATION IN IDIOPATHIC STEATORRHEA

## II THE ORIGIN OF THE LOW BLOOD SUGAR CURVE<sup>\*</sup>

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In a preceding paper<sup>1</sup> the "low blood sugar curve" was defined as a curve with a rise of only 40 mg per hundred cubic centimeters or less after the ingestion of about 60 Gm of dextrose, provided that the determination was made by Hagedorn and Norman-Jensen's method and that the blood was drawn at intervals of from ten to fifteen minutes. Further, it was pointed out that the low blood sugar curve occurred frequently in the idiopathic steatorrheas, and its clinical significance was discussed. In this paper, I shall report some investigations that I made in order to understand how the low blood sugar curve comes about.

Assuming that the symptoms of the idiopathic steatorrheas arise from some disturbance in absorption which applies chiefly to the alimentary fats but perhaps also, in lesser degree, to the proteins, one might imagine that the slight rise of the blood sugar curve after the ingestion of dextrose is due to a lowered absorption of dextrose or, as Herter<sup>2</sup> assumed in the case of Gee-Heiter's disease, to a destruction of dextrose through abnormal bacterial action. This theory is suggested by the fact set forth in the preceding paper, that the blood sugar curve is normal in the cured patients, and that it rises in the good periods of the disease. As low blood sugar curves, however, may occur in these periods with normal stools (patients 2 and 4, table 3), of which the curve in the accompanying chart is a good illustration, and as a normal curve may be found during a period of severe fatty diarrhea (patient 7, table 3), the observations indicate that the rise of the blood sugar curve is a phenomenon concurrent with improvement in the absorption of fat.

To evade the influence which a lowered absorption or a destruction of dextrose in the intestines might have on the form of the blood sugar curve, I gave intravenous injections of 20 Gm of dextrose to

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<sup>\*</sup> Submitted for publication, Feb 11, 1929.

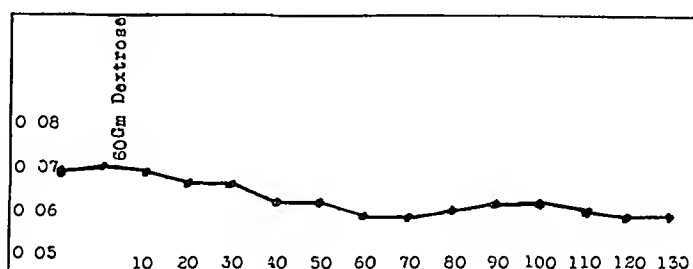
<sup>\*</sup> From the Medical Department of St Elizabeth's Hospital.

1 Thaysen, T E H, and Norgaard, A. The Blood Sugar Regulation in Idiopathic Steatorrhea. I. The Low Blood Sugar Curve, *Arch Int Med* **44** 17 (July) 1929.

2 Herter. *Intestinal Infantilism*, New York, The Macmillan Company, 1908.

six patients. The injection time was from two to three minutes. Four of the six patients (cases 2, 4, 10 and 5) showed a low curve on some of the tests, the others showed a low curve on every test.

Table 1 shows that in three of the cases, the tolerance figure, which is calculated after Stephan Jorgensen's<sup>3</sup> formula, is lower than any which he demonstrated in patients with normal carbohydrate metabolism, in whom the lowest loading figure was 49. The fourth patient with a low curve (case 2) showed a normal loading figure. The loading figure is also normal in case 6 (with a low level curve) and in case 8 (with a normal curve after the ingestion of dextrose). Leaving



Blood sugar curve for patient 6, showing no rise whatever but instead, a slight fall after the ingestion of dextrose. This would seem to indicate that the patient did not take the dextrose. The assistant observed, however, that she drank the solution of dextrose after which she was nauseated, as she had been after the ingestion of dextrose on previous examinations. Figures along bottom of chart indicate minutes.

TABLE 1—*Tolerance Figures After the Intravenous Injection of 20 Gm of Dextrose*

Patient Number	Age	Sex*	Rise of Blood Sugar After the Ingestion of Dextrose, Milligrams per Hundred Cubic Centimeters	Tolerance Figure After the Injection of 20 Gm Dextrose	Comment
2	43	♀	20 28 27	121	Nontropical sprue
4	38	♀	39 38 37	42	Nontropical sprue
5	36	♂	54 40 58 50 39	48	Nontropical sprue
6	53	♂	55 53	116	Nontropical sprue
8	56	♀	85 73	93	Nontropical sprue Almost free from symptoms
10	47	♂	21 51	42	Tropical sprue

\* In this and the following tables the female sex is indicated by ♀, the male sex by ♂.

out patient 8, there is an average loading figure of seventy-four in five patients with low or low level curves, while Joergensen found an average loading figure of 107 in thirty-two normal persons and, later (not published), an average of 113 in thirteen normal persons. Taking the group as a whole, three of six curves are abnormally low and fall rapidly to the fasting value. That agrees with the frequency of the low blood sugar curve in the tests after the ingestion of dextrose (50 per cent).

Although these observations definitely indicate that the cause of the low blood sugar curve is not to be found in a decrease or impairment

TABLE 2—*The Respiratory Quotient Before and After the Ingestion of 70 Gm of Dextrose*

Patient Number	Age	Sex	Respiratory Quotient Before Ingestion of Dextrose	Respiratory Quotient After Ingestion of 70 Gm of Dextrose	Date (1928)	Comment
2	43	♀	0.75 0.75	0.92	5/15	Nontropical sprue, bad period
4	38	♀	0.85 0.85	0.96 0.96	5/19	Nontropical sprue, bad period
5	36	♂	0.81 0.81	0.99 0.97	3/15	Nontropical sprue, fairly good period steatorrhea persisting
6	32	♂	0.83 0.86	1.00 0.98	7/15	Nontropical sprue, bad period
7	37	♀	0.98 0.98	1.02 1.02	5/25	Nontropical sprue, good period
8	36	♂	0.76 0.75	0.87 0.87	6/19	Nontropical sprue, good period
9	11	♀	0.88 0.87	0.91 0.91	12	Gee Herter's disease, bad period
10	17	♂	0.81 0.81	0.93 0.85	5/16	Tropical sprue, good period

\* 1 hour after the ingestion of dextrose

of the absorption of dextrose, I have tried further to establish this view by investigating whether the respiratory quotient<sup>4</sup> increases in these patients after the ingestion of dextrose.

Table 2 shows that the respiratory quotient, determined after twelve hours' fasting, rises as in normal persons to or nearly to the straight quotient of carbohydrate oxidation, three quarters of an hour after the ingestion of about 70 Gm of dextrose in about 700 cc of water. This shows that the ingested dextrose must have been absorbed.

The cause of the low blood sugar curve, therefore, cannot be defective absorption or destruction of the dextrose. It may be looked

4 The respiratory quotient is determined with the self-registering respiratory apparatus, constructed by Hagedorn (Biochem J **18** 1301, 1924). In clinical investigations, this apparatus has the particular advantage that instances of uneven ventilation can be detected. All doubtful observations have been discarded.

for, then, in abnormal metabolism of dextrose. In view of the fact that the body is deprived of a greater or smaller part of its energy through the loss of fats in the stools, it would seem reasonable to assume that the organism utilizes the absorbed carbohydrates to a larger extent than normal instead of storing them as glycogen. If this explanation holds true, one must assume that the deposits of glycogen in the organism are smaller than normal. In order to find out if this is the case I determined the respiratory quotient in some of these patients after an ordinary diet of their choice, but rather low in fats, and after a diet high in carbohydrates (Hagedorn, Holten and Hecht-Johansen<sup>5</sup>), with the addition of 100 Gm of fish and 10 Gm

TABLE 3—*The Respiratory Quotient on Ordinary and Carbohydrate-High Diet*

Patient Number	Age	Sex	Date (1928)	Respiratory Quotient Ordinary Diet	Date (1928)	Respiratory Quotient, Carbohydrate Diet	Comment
2	43	♀	3/9	0.75 0.74	5/15	0.75 0.75	Did not feel well, febrile during experiment (June 15, 1928)
4	38	♀	3/8	0.83 0.83	5/19	0.85 0.85	
5	36	♂	3/13	0.81 0.80	5/24	1.03	Did not feel well during experiment (June 24, 1928)
6	53	♂	3/15	0.89 0.86	6/27	0.88	
7	57	♀			5/25	0.98 0.96	
8	56	♀	3/16	0.78 0.78	6/19	0.76 0.76	
9	11	♀	3/12	0.88 0.87			
10	47	♂	5/11	0.81 0.81	6/16	0.84 0.84	
Average				0.817		0.850	

of butter. These diets were given two days preceding the examination that was made after twelve hours of fasting. The results are given in table 3.

Table 3 shows that when the patient is on an ordinary diet the average value of the respiratory quotient is 0.817, which is so high that even on that diet the organism must have a considerable amount of carbohydrate in reserve. On a diet high in carbohydrates the average value of the respiratory quotient rises to 0.85, which agrees with the average respiratory quotient in normal persons on the same diet. According to Hagedorn, Holten and Hecht-Johansen, this is  $0.864 \pm 0.009$ . These tests, then, do not indicate that in these patients the organism is particularly poor in glycogen, or that it is incapable

<sup>5</sup> Hagedorn, H. C., Holten, C., and Hecht-Johansen, A. Pathology of Metabolism in Obesity, Arch Int Med 40:30 (July) 1927.

of storing carbohydrates as glycogen. I may add that the ingestion of dextrose after an ordinary diet or one high in carbohydrates produced no sign that the patients converted carbohydrates into fats to any larger extent than normally. I further investigated whether these patients were capable of mobilizing their carbohydrate stores on injection of epinephrine (1 mg subcutaneously). As shown in table 4, I found a rise in the blood sugar curve that was rather high when compared with the observations of Brems,<sup>6</sup> Billinghamer,<sup>7</sup> Brosalmer<sup>8</sup> and Kylan.<sup>9</sup>

TABLE 4—*Rise in the Blood Sugar Curve After Injection of 1 Milligram of Epinephrine*

Patient Number	Age	Sex	Rise in Milligrams per Hundred Cubic Centimeters After the Ingestion of Dextrose	Rise in Milligrams per Hundred Cubic Centimeters After Injection of 1 Cc of Epinephrine	Urine, Sugar	Comment
2	43	♀	20 23 27 40	90	Negative	Nontropical sprue
4	38	♀	30 38 37	114	Positive	Nontropical sprue
5	36	♂	51 10 38 50 39	68	Negative	Nontropical sprue
A. L.	4		32 16	70	Negative	See Herter's disease *

\* I am indebted to Dr. Ellen Svendsgaard for making this determination.

#### COMMENT

By these observations, it is demonstrated that the low blood sugar curve in idiopathic steatorrhea cannot be due to defective absorption or destruction of dextrose in the intestines. Further, it cannot be occasioned by a marked systemic deficiency of glycogen. By this method of exclusion, one arrives at the view that the low blood sugar curve must be due to some disturbance in the regulation of the blood sugar.

Considering that a low blood sugar value during fasting is found more frequently in idiopathic steatorrhea than normally, although hypoglycemic values are rather rare, and that the low blood sugar curve may be interpreted as an alimentary relative hypoglycemia, one might expect to find the same low blood sugar curve in the cases of

6 Brems. *Acta med Scandinav* **64** 547, 1926.

7 Billinghamer. *Deutsches Arch f klin Med* **136** 1, 1921.

8 Brosalmer. *Deutsches Arch f klin Med* **137** 299, 1921.

9 Kylan. *Zentralbl f inn Med* **45** 745, 1924.

spontaneous hypoglycemia that are reported in the literature. This is further suggested by the fact that patients with idiopathic steatorrhea often complain of excessive fatigue and have marked nervous disturbances and periodic attacks of a remarkably severe sensation of hunger, symptoms which are also found, although in a somewhat different form, in patients with spontaneous hypoglycemia. While these symptoms occur periodically in idiopathic steatorrhea, the nervous symptoms and the frequent but not constant sensation of hunger in spontaneous hypoglycemia seem to appear at definite times of the day, usually some time after meals and coinciding with the abnormally low blood sugar values.

In those cases, however, in which the hypoglycemia is attributed to a lesion of the liver (Wagner and Parnas,<sup>10</sup> Schnapper and van Crefeld,<sup>11</sup> and, perhaps, Laroche, Lelourdy and Bussière<sup>12</sup>), there is no low blood sugar curve after the ingestion of dextrose but, instead, a normal (Schnapper and van Crefeld and Laroche) or an abnormally high rise (Wagner and Parnas). Wilder, Allan, Power and Robertson<sup>13</sup> found a similar abnormally high rise of the blood sugar curve in a case of spontaneous hypoglycemia that was thought to be due to hyperinsulinism produced by a metastasizing carcinoma originating in the islands of Langerhans. In those cases (Stenstrom,<sup>14</sup> Odin<sup>15</sup> and Petterson<sup>16</sup>), in which the hypoglycemic coma is regarded as due to a disturbance of the blood sugar regulation that is exerted by the thyroid gland, the suprarenal glands and the insular tissue of the pancreas (on autopsy, Odin and Petterson found atrophy of the thyroid and suprarenal glands, together with increase of the pancreatic islands), the blood sugar curve<sup>17</sup> was found to be normal (Stenstrom) or questionably low. (In a test made every twenty minutes by Odin and Petterson there was a rise of 31 and 34 milligrams per hundred cubic centimeters.) Also in those cases in which the origin of the hypoglycemia was doubtful (Harris,<sup>18</sup> Cammidge,<sup>19</sup> Sendrail and

10 Wagner and Parnas. *Ztschr f d ges exper Med* **25** 361, 1921

11 Schnapper and van Crefeld. *Bull et mem Soc med d hôp de Paris* **52** 1, 1928

12 Laroche, Lelourdy, and Bussière. *Presse med* **36** 513, 1928

13 Wilder, R M, Allan, F N, Power, M H, and Robertson, H E. *Carcinoma of the Islands of the Pancreas*, *J A M A* **89** 348 (July 30) 1927

14 Stenstrom. *Deutsches Arch f klin Med* **152** 173, 1926

15 Odin. *Acta med Scandinav*, supplement no 26, 1928, p 182

16 Petterson. *Acta med Scandinav* **69** 232, 1928

17 No blood sugar curve is given by Gougerot and Peyre. *Compt rend Soc de biol* **93** 1202, 1925

18 Harris, S. *Hyperinsulinism and Dysinsulinism*, *J A M A* **83** 729 (Sept 6) 1924

19 Cammidge. *Lancet* **2** 1227, 1924

Planques<sup>20</sup>), there was a normal blood sugar curve. The injection of epinephrine in these cases caused a slight rise of the blood sugar curve (Wilder, Wagner and Parnas,<sup>10</sup> Schnapper and van Crefeld,<sup>11</sup> Stenstrom,<sup>14</sup> Odin<sup>15</sup> and Petterson<sup>16</sup>). In my own cases of idiopathic steatorrhea, the blood sugar curve was rather high after the injection of epinephrine.

While no typical low blood sugar curve was encountered in the aforementioned cases of spontaneous hypoglycemia, and, as far as I know, curves of this kind are not particularly numerous in monoglandular lesions such as myxedema, Addison's disease and hypophyseal lesions, the literature contains several reports of low blood sugar curves in experimental hyperinsulinism (Mansfeld,<sup>21</sup> Albern and Beguslow<sup>22</sup> and Jorns<sup>23</sup>). These authors have shown that the oral administration of dextrose in dogs and rabbits is followed by blood sugar curves that are considerably lower some time after the ligation of Wirsung's duct or after twisting of the pancreas than before the operation. This operation brings about a more or less pronounced atrophy of the pancreas and, as Heineheimer has particularly demonstrated in the chicken, hypertrophy of the islands of Langerhans with an increase of the insulin content.

These experiments demonstrate excellently the influence that an increase in the production of insulin may have on the course of the blood sugar curve. As could be expected, these conditions are much more complicated in human pathology than in experiments on animals and they offer no dependable contribution to the understanding of how the low blood sugar curve occurs in idiopathic steatorrhea. For the present, one can merely state that the low blood sugar curve in idiopathic steatorrhea is due to an abnormality of the blood sugar regulation, and that no associated changes have been demonstrated in the liver, the organ of most importance in carbohydrate metabolism.

In seeking the cause for the disturbance in the regulation of the blood sugar that underlies the low blood sugar curve, it is reasonable to associate it with that state of undernutrition in which patients with idiopathic steatorrhea usually have been for several years. Table 3 in the preceding paper<sup>1</sup> seems to confirm this view to some degree, as the blood sugar curve is normal in well-nourished patients (patients 7, 8 and 12) and low in these poorly nourished. The table shows, however, that there is no definite demonstrable relation between the deficit in weight and the height of the blood sugar curve. In case 4, for instance,

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20 Sendrail and Planques. *Gaz d hôp* **100** 1105, 1927.

21 Mansfeld. *Klin Wchnschr* **3** 2378, 1924.

22 Albern and Beguslow. *Klin Wchnschr* **7** 586, 1928.

23 Jorns. *Klin Wchnschr* **5** 2452, 1926.



the weight of the patient was almost normal in spite of the low curve, in case 5, the curve did not rise in spite of a considerable gain in weight, in case 6, it did not fall in spite of a loss of weight, and in case 10, the increase in rise of the curve was not connected with any gain in weight. Add to this the fact that the patients with high curves showed considerable clinical improvement and one might just as well associate the greater rise of the curve with the clinical improvement. This material, therefore, does not indicate any particularly definite relation between the nutrition of the patients and the height of the blood sugar curve.

Recent investigations of the influence of a brief fast on the rise of the blood sugar curve showed that the rise is greater after fasting up to three days (Traugott<sup>24</sup>). As is well known, undernutrition for a longer period is often associated with mild glycosuria after meals ("Vakantglykosuri," Hoppe-Seyler<sup>25</sup> and "Hungerdiabetes," Hofmeister<sup>26</sup>), a form of glycosuria which Nothmann and Cobet<sup>27</sup> regarded as renal, and which was not connected with any low blood sugar curve in their experiments on animals. So far as I know, there are no usable data on the form of the blood sugar curve in the hunger edema that occurred in Germany during the war. Jansen<sup>28</sup> stated that in this case the amount of blood sugar during fasting was either normal or a little below normal. In carcinoma of the digestive tract, which often produces protracted and marked undernutrition, Friedenwald and Grove<sup>29</sup> found that the blood curve rises higher and falls more slowly than it does normally, and that the blood sugar value during fasting is higher than usual. These investigations, however, are hardly conclusive as to the influence of undernutrition on the rise of the blood sugar curve, because in idiopathic steatorrhea the undernutrition is protracted for a much longer period than in the aforementioned conditions. Also, as is well known, chronic inanition causes loss of weight and, to some extent, changes in the endocrine glands with the exception, apparently, of the pancreas (Jackson<sup>30</sup>). In view of the fact that the parathyroid glands (tetany), the suprarenal glands (low blood pressure, abnormal pigmentation) and, eventually, the thyroid gland (increase of basal metabolism to 143 per cent) are not infrequently affected in cases of idiopathic steatorrhea, the question arises as to whether that disease of the endocrine glands regulating the blood sugar which supposedly underlies

24 Traugott *Klin Wchnschr* **1** 892, 1922

25 Hoppe-Seyler *Verhandl d Kong f inn Med* 1902, p 384

26 Hofmeister *Arch f exper Path u Pharmacol* **26** 355, 1896

27 Nothmann and Cobet *Verhandl d deutsch Gesellsch f inn Med, Kong* 40 1928, p 246

28 Jansen *Deutsches Arch f klin Med* **131** 144, 1920

29 Friedenwald and Grove *Am J M Sc* **160** 313, 1920

30 Jackson *Inanition and Malnutrition*, London, J & A Churchill, 1925

the low blood sugar curve is not occasioned by the same noxious factor that causes the aforementioned functional disturbances of the endocrine glands

#### SUMMARY

The low blood sugar curve in idiopathic steatorrhea cannot be due to defective absorption or destruction of dextrose in the intestinal tract for the following reasons

- 1 The blood sugar curve is low just as often after intravenous injection of dextrose as after intake by mouth

- 2 The respiratory quotient rises to about one after the ingestion of dextrose

- 3 The respiratory quotient is higher on a diet of carbohydrates than on an ordinary diet

The low blood sugar curve cannot be due to an increased oxidation of carbohydrates, caused by the loss in fats, as the respiratory quotient on an ordinary diet shows that the organism has a fair reserve supply of carbohydrates

The low blood sugar curve does not occur more frequently in cases of chiefly monoglandular endocrine lesions or in spontaneous hypoglycemia than it does in normal persons. On the other hand, it can be produced in dogs by ligating the duct of Wirsung or by twisting the pancreas

The cause of the low blood sugar curve is uncertain. It can hardly be undernutrition, more probably it is due to some toxic effect on the endocrine glands which regulate the blood sugar content

# RENAL INSUFFICIENCY ASSOCIATED WITH BENCE-JONES PROTEINURIA

REPORT OF THIRTEEN CASES WITH A NOTE ON THE CHANGES  
IN THE SERUM PROTEINS \*

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The frequency of the occurrence of renal insufficiency in the presence of Bence-Jones proteinuria deserves further emphasis. Geschickter and Copeland<sup>1</sup> recently called attention to the close association of multiple myeloma, Bence-Jones proteinuria and renal disease, stating that the changes in the kidney in cases of multiple myeloma are as varied and diverse as the pulmonary changes, and that they are present in a larger proportion of the cases, about 70 per cent. If this statement is accepted, it must be remembered that these statistics regarding the presence of renal changes are based primarily on postmortem data. Most of the cases of multiple myeloma, approximately 80 per cent, occur in patients between the ages of 40 and 70 years, with the peak of incidence at 55 years. Therefore, some of the abnormalities found in the kidney, post mortem, may be entirely incidental and not the direct result of either the multiple myeloma or the proteinuria. On the other hand, the association of the two conditions is too common and the clinical and pathologic descriptions are too characteristic, as a rule, to be explained on the basis of coincidence. Some causal relationship must exist.

We have selected from the files of the Mayo Clinic thirteen cases of Bence-Jones proteinuria with evidence of some renal insufficiency. This probably does not represent the entire series, as several patients were allowed to go home after the diagnosis of multiple myeloma had been made without undergoing any further studies from the standpoint of renal function, and therefore, the data are incomplete for the text of this discussion. This factor also precludes a statement on our part as to the actual frequency of association of the two conditions. Some of these cases were included in the previous reports of

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\* From the Division of Medicine, the Mayo Clinic

1 Geschickter, C F, and Copeland, M M. Multiple Myeloma, Arch Surg 16 807 (April) 1928

Walters<sup>2</sup> and Meyerding.<sup>3</sup> Only the significant data relative to the renal function are included in the abstract of the case histories of the previously reported cases. Two additional cases, without renal insufficiency, are reported because of the studies on the serum proteins.

#### REPORT OF CASES

CASE 1—A man, aged 47, came to the Mayo Clinic on Oct. 18, 1921, complaining of weakness and soreness in the limbs and neck. The patient apparently had been in good health until September, 1920. At that time, however, he had begun to have sharp pains in the back, radiating to the left side and left lower quadrant of the abdomen. He had been under treatment in the hospital for a few weeks for nephritis, although urinary symptoms or edema had not been present at that time. There had been gradual recovery in the spring of 1921 with a gain in weight and strength, although on several occasions he had been unable to urinate and catheterization had been necessary. A second similar attack of left-sided pain had been noted in June, 1921, at which time he had had fever for a short time, on several occasions as high as 104° F. He had been in bed for two months complaining of weakness, gas on the stomach, slight diarrhea and occasional attacks of vomiting. There had been no pain since then, but there had been tenderness on both sides of the abdomen and soreness along the legs, arms and neck. The home physician had found Bence-Jones protein in the urine a few days before admission to the clinic, and had advised study here.

The patient was found to be anemic and pale. The heart was slightly enlarged to the left, and there was a slight systolic murmur at the apex. A moderate grade of arteriosclerosis of the brachial arteries was noted. There was some pigmentation over the thorax, and especially around the genitalia and anal fold. There was no edema. Urinalysis disclosed Bence-Jones proteinuria, and, also, moderate albuminuria. The urinary sediment usually was clear, but on a few occasions it contained erythrocytes, casts and pus cells. The maximal excretion of phenol-sulphonphthalein obtained on three occasions was 5 per cent in two hours. The blood urea was 218 mg., the uric acid 7.7 mg. and the creatinine 7.5 mg. per hundred cubic centimeters. The erythrocytes numbered about 2,000,000 per cubic millimeter of blood, and the hemoglobin by the Dare method was about 35 per cent. The leukocytes numbered from 5,000 to 7,500 per cubic millimeter of blood. The blood pressure varied from 110 to 145 systolic and from 60 to 100 diastolic, measured in millimeters of mercury. There was fixation of the specific gravity of the urine. The ocular fundi were essentially normal, except for the anemic appearance and some choroidal sclerosis. The blood serum and spinal fluid were tested for the presence of Bence-Jones protein, with negative results. The Wassermann reaction of the blood was negative. Fractional analysis of gastric content revealed absence of free hydrochloric acid after a test meal. Roentgenograms of the stomach gave evidence of a duodenal ulcer, whereas that of the chest disclosed slight enlargement of the heart. Roentgenograms of the head, spinal column, pelvis, both shoulders, arms and forearms, both femurs, accessory nasal sinuses,

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2 Walters, Waltman. Bence-Jones Proteinuria. A Report of Three Cases with Metabolic Studies, *J. A. M. A.* **76** 641 (March 5) 1921, Chronic Nephritis with Bence-Jones Proteinuria. Effect of Radium Exposures on Quantitative Output of Bence-Jones Protein, *M. Rec.* **100** 847, 1921.

3 Meyerding, H. W. Multiple Myeloma, *Radiology* **5** 132, 1925.

TABLE 1—Data Concerning Thirteen Cases of Renal Insufficiency Associated with Bence-Jones Proteinuria

Case	Sex	Age, Years	Urine					Blood					Blood Pressure, Mm of Mercury		Edema	Retinitis		
			Proteinuria	Hematuria	Casts	Pyuria	Excretion of Phenol-sulphonphthalein in 2 Hours, per Cent	Specific Gravity	Blood Urea, Mgs per 100 Cc	Blood Creatinine, Mgs per 100 Cc	Average Hemoglobin, per Cent (Dare)	Erythrocytes, Millions per Cc of Blood, Average	Leucocytes per Cc of Blood, Average	Systolic			Diastolic	
1	M	47	+++	++	++	++	Pyuria	5	+++	218	7.5	36	1.95	6,500	110-145	60-100	0	0
2	F	59	+++	++	++	++	++	10	++	132	18	83	1.83	6,000	180-210	100-110	0	Arteriosclerosis
3	M	68	+++	+	0	+	++		++	115	9.2	50	3.08	7,000	120	70	0	
4	F	42	+++	0	0	++	++	10	++	109	7.5	57	2.95	7,000	125-140	80	0	0
5	M	49	+++	0	+	++	++	15	++	81		50	3.56	5,600	145	85	0	Slight arteriosclerosis
6	M	43	+++	0	0	0	0	25	++	66	3.8	82	1.86	6,000	115-125	45	0	0
7	F	52	+++	++	+	1	++	30	++	66	2.5	55	3.00	7,250	115	70	0	0
8	M	60	+++	++	++	+	++		++	62		50	2.80	7,900	175-210	115-135	0	Arteriosclerosis
9	F	61	+++	++	0	+++	++	10	++	46		45	2.84	14,300	185	105	0	
10	M	64	+++	0	++	++	++	25	++	50	2.4	42	2.60	5,800	100	65	0	0
11	M	56	+++	+	+	++	++		++	50	2.3	47	2.80	6,200	130-110	70-80	0	++
12	F	70	+++	0	0	0	0	35	++			60	3.65		130	70	+	history
13	M	55	+++	0	0	0	0	15	+	33	1.8	51	3.60	6,500	120-140	70-85	0	0

\* 0 = none, ±very slight, + mild, ++ moderate, +++ severe

There was no edema and in the urinary sediment were no erythrocytes, but there was a considerable number of casts and some pus cells

CASE 6 (Meyerding)—A man, aged 43, came to the clinic on Oct 29, 1923, complaining of weakness, drowsiness and loss of weight

The urine contained Bence-Jones protein, and roentgenograms of the osseous system revealed multiple areas of bone destruction in the humeri, upper end of the left radius and ulna, left tibia and ribs. A diagnosis of multiple myeloma with Bence-Jones proteinuria was made. Laboratory data are summarized in table 1. A diagnosis of associated renal insufficiency was made for several reasons. Excretion of phenolsulphonphthalein was only 25 per cent in two hours. Moreover, the blood urea was 62 to 66 mg, the uric acid, 5.2 mg, and the creatinine, 3.8 mg per hundred cubic centimeters. There was also a definite tendency toward fixation in the specific gravity of the urine. The serum protein was 6.5 and 7.3 per cent. There was no edema. The blood pressure was from 115 to 125 systolic and 45 diastolic. Examination of the fundi gave essentially negative results.

CASE 7—A woman, aged 52, was admitted to the clinic on Nov 15, 1923, because of discomfort in the lower portion of the abdomen, and to have an investigation of an albuminuria. About two years before admission she had been knocked down on a stone floor, striking on her right hip and back. She had suffered severe nervous shock and, according to her description, had been completely paralyzed, unable to move hands, head or feet, yet, she had retained perfect control of the sphincters. Movement in the upper extremities had returned rapidly, but for three weeks she had not been able to move her legs. Then she gradually had improved and had left her bed. However, she had experienced great difficulty in moving about and convalescence had been prolonged because of nervousness and weakness. She never had felt entirely well since that time, and always had had some weakness and pains in the back, across the sacro-iliac region and between the shoulders.

General examination showed the patient to be considerably underweight, and anemic, with moderate kyphosis. The heart was not enlarged and was not grossly abnormal, a systolic bruit was audible over the apex. In other respects, also, general examination gave entirely negative results except for large uterine fibromyomas. The blood pressure was 115 systolic and 70 diastolic. Urinalysis disclosed marked proteinuria. The erythrocytes numbered from 2,600,000 to 3,400,000 and the hemoglobin, by the Dare method, was from 50 to 60 per cent. The leukocyte count was normal. The excretion of phenolsulphonphthalein was 30 per cent in two hours. Blood urea was 66 mg and creatinine 2.5 mg per hundred cubic centimeters. The Wassermann reaction of the blood was negative. Examination of the fundi gave negative results. There was no edema. Because of the unusual renal data, the urine was examined for Bence-Jones protein, and a positive reaction was obtained. Roentgenograms disclosed multiple areas of destruction in the bones of the head including the skull, in the ribs and in both clavicles. The bones of the extremities were not involved. A diagnosis was made of multiple myeloma, with Bence-Jones proteinuria and associated secondary anemia and renal insufficiency.

CASE 8—A man, aged 60, was admitted to the clinic on Oct 1, 1928, complaining chiefly of difficulty in walking, of six months' duration. Three or four years before admission he had had headaches, occurring once or twice a week and associated frequently with nausea and vomiting, but in the last six or eight months he had had little headache. One year previously, he had noticed a lump

over the upper part of the sternum. This had increased in size. For five or six months he had had shooting pains in the lower portion of the chest. Six months previously he had sprained his back while swinging at a golf ball, and had been disabled for some time as a result of this. In May, 1928, he had had a sudden pain in the back and had fallen to the ground without losing consciousness. He had been unable to stand, had crawled to the house on his hands and knees, and had been confined to his bed for twelve weeks, chiefly because of pain in the back, and in the chest. Gradually weakness had developed in both arms and legs and definite incoordination, with some difficulty in speech, had appeared in the last two months. More recently he had noticed considerable loss of weight and frequency in urination.

The patient was tall, thin and anemic. He showed evidence of loss of weight and strength and was somewhat ataxic. There was a large swelling in the upper end of the sternum approximately 9 cm in diameter. General examination otherwise did not disclose abnormalities. There was no edema. The blood pressure varied from 175 to 210 systolic and from 115 to 140 diastolic. Urinalysis revealed marked Bence-Jones proteinuria, a few hyaline casts, erythrocytes and pus cells. The hemoglobin by the Dare method was 48 per cent, erythrocytes numbered 2,800,000 and leukocytes, 7,900. Blood urea was 62 mg per hundred cubic centimeters. The Wassermann reaction of the blood was negative and examination of the spinal fluid gave negative results. Examination of the fundi disclosed only moderate arteriosclerosis of the hypertensive type. Roentgenograms of the chest gave evidence of diffuse dilatation of the arch of the aorta with a circumscribed shadow at the level of the second rib anteriorly. Roentgenograms of the head and of the lumbar and thoracic spine revealed multiple areas of destruction, probably multiple myeloma. A diagnosis was made of multiple myeloma with Bence-Jones proteinuria and associated renal insufficiency, secondary anemia, arteriosclerosis and hypertension, and an intracranial lesion, not definitely explained but probably associated with the multiple myeloma.

CASE 9—A woman, aged 69, was admitted to the clinic on Aug 16, 1927, complaining chiefly of generalized aches and pains and weakness of about eight months' duration. This weakness had been steadily progressive, and associated with it there was a loss in weight of between 50 and 60 pounds (227 and 272 Kg). The pain affected chiefly the lumbar and lower abdominal regions and was becoming progressively worse, so that at times she could not walk. Shortly before she had come to the clinic she had noticed progressive dyspnea, but there had never been any edema. She had been voiding urine every half hour in small amounts during the day, and frequently at night.

At the time the patient was examined she was cachectic. Her heart was slightly enlarged, and there was an accentuated aortic second sound. Movement was extremely painful and some tenderness over the lower part of the abdomen was noted. The blood pressure was 185 systolic and 105 diastolic. Urinalysis disclosed marked proteinuria, and a positive Bence-Jones reaction was obtained. An uncatheterized specimen contained a few erythrocytes and considerable pus, but a catheterized specimen gave evidence only of marked pyuria. The hemoglobin was 45 per cent by the Dare method, the erythrocytes numbered 2,840,000 and leukocytes numbered 14,000. The Wassermann reaction of the blood was negative. Analysis of gastric content gave negative results. Excretion of phenol-sulphonphthalein was 10 per cent in two hours. The blood urea was 46 mg per hundred cubic centimeters. Roentgenograms of the stomach did not disclose abnormalities and in a roentgenogram of the chest the only abnormality was some

cardiac enlargement. Roentgenograms of the head, long bones and spine gave evidence of multiple areas of bone destruction suggestive of multiple myeloma. A diagnosis was made of multiple myeloma with Bence-Jones proteinuria and associated renal insufficiency, arteriosclerosis, hypertension, cystitis and probably pyelonephritis.

CASE 10—A man, aged 64, came to the clinic on May 22, 1924, complaining of weakness and dyspepsia. Two years before admission the patient had been struck by an automobile, and the right hip was fractured, the sacrum was bruised and the head injured. He had been in bed for five months as a result of this accident, and had not regained normal strength until a year later. Then, however, he had begun to feel normal, had regained his appetite, had resumed his work and had felt as well as he ever had until about four months before admission, when he had begun to have a dyspepsia such as that caused by peptic ulcer. Since that time, also, there had been gradual loss of strength, a loss of 10 pounds (4.5 Kg.) in weight, and he had become pale and anemic. He had been obliged to urinate three or four times at night in recent months.

The patient was anemic and emaciated, and arcus senilis was present. The heart and lungs seemed normal except for emphysema. Other significant abnormalities were not noted except for enlargement, deformity and ankylosis of the right hip joint. There was some hypertrophy of the muscles of the right thigh, and a scar over the sacrum posteriorly as a result of the old injury. The blood pressure was 100 systolic and 65 diastolic. Marked Bence-Jones proteinuria was found on urinalysis, but only an occasional pus cell was found otherwise. The Wassermann reaction of the blood was negative. Examination of the fundi gave essentially negative results. Erythrocytes numbered from 2,400,000 to 2,800,000, hemoglobin was 40 to 45 per cent by the Dare method, and leukocytes numbered from 5,000 to 8,000. Excretion of phenolsulphonphthalein was 25 per cent in two hours. Blood urea was 50 mg., nonprotein nitrogen was 74, the uric acid, 45, and the creatinine, 24 mg. per hundred cubic centimeters. Definite inability to concentrate the urine was noted. The serum protein was 6 per cent. Analysis of gastric content disclosed slight hyperacidity. Roentgenograms of the stomach revealed a perforated duodenal ulcer, and other roentgenograms showed that there was extensive malignancy in the bones of the skull, marked hypertrophic arthritis of the spine with destruction of the ribs, probably malignant, and flattening of the head of the right femur. The long bones seemed normal. A diagnosis was made of multiple myeloma, renal insufficiency, perforated duodenal ulcer and hypertrophic arthritis.

CASE 11 (Meyerding)—A farmer, aged 56, came to the clinic on Aug. 3, 1923, complaining of pain in the chest of four months' duration following injuries received in a fall from a wagon. He had sustained a second injury of the chest a few days before coming for examination, when a cow had kicked him. A diagnosis of multiple myeloma was made based on the presence of Bence-Jones proteinuria, secondary anemia, history and roentgenograms. The roentgenologic interpretation was hypertrophic arthritis of the spine and lesion of the eighth rib, due to an injury or myeloma.

The results of the laboratory examination as reported by Meyerding are summarized in table 1, as follows. Blood pressure was from 130 to 140 systolic and from 70 to 80 diastolic, there was marked Bence-Jones proteinuria, urinalysis revealed occasional hyaline casts, erythrocytes and pus cells. The blood urea was 50 mg., the creatinine 23 mg., and the uric acid 57 mg. per hundred cubic centimeters. Erythrocytes numbered from 2,500,000 to 3,000,000, with hemoglobin



from 45 to 55 per cent by the Dare method, the leukocytes numbered from 5,000 to 7,000. There was no edema. Some tendency toward fixation of the specific gravity of the urine was noted. Examination of the fundi disclosed some arteriosclerosis and two small hemorrhages suggestive of the anemic type of hemorrhage. The basal metabolic rate was +14. The blood from this patient showed marked autoagglutination in the laboratory. There undoubtedly was some change in the serum proteins, but the report of analysis unfortunately was lost.

CASE 12—A woman, aged 70, registered at the clinic on Aug 7, 1928. Six months before admission she had complained of severe pain high in the back and some swelling of the ankles. Urinalysis had revealed large amounts of "albumin," and a diagnosis of chronic nephritis had been made. Since that time marked weakness had developed progressively with loss in weight and strength, nausea, vomiting, diarrhea and a sensation of heaviness and drawing over the lower part of the abdomen. For some time she had noted shortness of breath, and palpitation on exertion.

Examination revealed a tall, thin, anemic, elderly woman. There was some dorsal kyphosis. The heart was enlarged slightly to the left and a systolic apical murmur was heard. There was some tenderness across the lower portion of the abdomen. The blood pressure was 130 systolic and 70 diastolic. There was no edema. Urinalysis disclosed marked proteinuria and a positive Bence-Jones reaction; microscopic examination of the urine gave entirely negative results. Hemoglobin by the Dare method was 60 per cent, erythrocytes numbered 3,650,000. Excretion of phenolsulphonphthalein was 35 per cent in two hours. There was a definite tendency toward fixation of specific gravity of the urine. Gastric content was normal to analysis. Roentgenograms of the stomach were negative. Roentgenograms of the skull and long bones gave evidence of multiple myeloma of the skull and humerus. A diagnosis was made of multiple myeloma, with Bence-Jones proteinuria, associated secondary anemia, and early renal insufficiency.

CASE 13—A man, aged 55, was admitted to the clinic on July 7, 1926, with a complaint of "sciatica." There was nothing significant in the family or personal histories except an attack of rheumatic fever at 11 years of age, and several mild attacks of influenza. The present illness began a year before admission when he strained his back while lifting. After a short period of disability, he was markedly improved until the latter part of March, 1926, when influenza was contracted. Following this, he began to have pains, across the lower part of the back, which were sharp and which radiated to the right hip. This pain was troublesome for a period of about two months, but from the end of that period had been less severe.

Examination revealed a well developed, well nourished man. The general examination was essentially negative except for marked prostatitis. The patient complained of soreness over the sacro-iliac joints and over the right hip and inguinal region. However, there was very little limitation of motion and crepitation was not noted. The blood pressure was from 120 to 140 systolic and from 70 to 85 diastolic, the temperature and pulse rate were normal. There was marked proteinuria. Microscopic examination of the urine was negative. Erythrocytes numbered from 3,200,000 to 3,800,000 and the hemoglobin by the Dare method ranged from 45 to 60 per cent. Leukocytes averaged about 6,500. Blood urea was 33 mg, the nonprotein nitrogen 40 mg and the creatinine, 18 mg per hundred cubic centimeters. Excretion of phenolsulphonphthalein was 45 per cent in two hours. Definite inability to concentrate urine was noted. There was no

edema Examination of the fundi gave essentially negative results The urine was examined for Bence-Jones protein because of the marked albuminuria and because of the anemia in the presence of only slight renal insufficiency, a positive Bence-Jones reaction was obtained in all specimens The serum proteins were determined on two occasions The total protein calculated from the refractive index was 10.75 and 10.55 and calculated from the total nitrogen, 10.08 and 10.54 per cent The albumin was 4 and 4.45 and the globulin 6.08 and 6.09 per cent Fractionation of the globulin by Howe's method gave euglobulin 4.4, pseudo-

TABLE 2—*Serum Protein in Cases of Bence-Jones Proteinuria*

Case and Author	Bence-Jones Protein	Total Serum Protein, Per Cent	Albumin, Per Cent	Globulin, Per Cent	Renal Insufficiency
1 *	0				+
2 *	+	9.00	2.50	6.50	+
4 *	+				+
6 *		7.30			+
10 *		6.00			+
13 *		10.54	4.45	6.09	±
14 *	+				0
15 *	+	7.00	5.26	1.74	0
Perlzweig, W. A., Delruc, G., and Geschickter, O. J. A. M. A. 90:755 (March 10) 1928					
Jacobson, V. C. J. Urol. 1:167 1917	+	13.15	4.06	9.09	+
Rowe, A. H. Arch. Int. Med. 19:351 (March) 1917	+	7.86†		7.86†	+
Hewitt, E. F. Lancet 1:66, 1929		6.80	4.8	2.0	
Case, O. E. Clifton M. Bull. 15:36, 1929	+	6.31	4.35	1.96	+
Thannhauser, S. J., and Krauss, F. Deutsches Arch. f. klin. Med. 133:183, 1920		5.27	4.54	0.73	+
Abderhalden, E. Ztschr. f. physiol. Chem. 106:130, 1919		6.41			+
d'Allocco, O. Lavori d. Cong. di med. int., 1899, pp. 258-266	+				+
Decastello, A. Ztschr. f. klin. Med. 67:319, 1909; Wein. Arch. f. inn. Med. 1:335, 1920	+				+
Donetti, E. Riv. crit. di clin. med. 2:789, 1901	+				+
Lllinger, A. Deutsches Arch. f. klin. Med. 61:255, 1898	+				±
Marcovici, E. E. Ann. Int. Med. 2:881, 1929	+				0
Taylor, A. E. Miller, C. W., and Sweet, J. E. J. Biol. Chem. 29:425, 1917	+				
Jochmann, G. and Schumm, O. Munchen. med. Wchnschr. 48:1340, 1901; Ztschr. f. klin. Med. 46:445, 1902	±				+
Askanazy, S. Deutsches Arch. f. klin. Med. 68:34, 1900	0				0
Ettles, D. Guy's Hosp. Rep. 77:104, 1907	0				±
Weber, F. P., Hutchinson, R., and Meleod, J. J. R. Am. J. M. Sc. 126:614, 1903	0				+
Reach, F. Deutsches Arch. f. klin. Med. 82:390, 1905	0				

\* Our series

† Reported as Bence-Jones protein, total protein not determined

globulin I, 1.14, and pseudoglobulin II, 0.55 per cent The relative viscosity was also increased, with readings of 3 and 2.85 Roentgenograms gave evidence of malignant destruction of the twelfth thoracic vertebra, with multiple areas of destruction in the bones of the pelvis, and involvement of the bones of the skull, probably multiple myeloma A diagnosis was made of multiple myeloma with Bence-Jones proteinuria, secondary anemia, and early renal insufficiency

We have also studied the serum proteins in two additional cases of Bence-Jones proteinuria in which careful clinical and laboratory

examination did not reveal evidence of renal insufficiency. These studies are reported in table 2 as cases 14 and 15. Case 14 has previously been reported by Walteis<sup>2</sup> and Wilson<sup>4</sup>. It is of especial interest because the Bence-Jones proteinuria had been recognized by the patient's physician three years before, yet there was no evidence of renal insufficiency. At necropsy elsewhere, the kidneys were reported to be grossly normal.

#### COMMENT

Many writers have emphasized the importance of examining the urine for Bence-Jones proteinuria in cases in which there is marked albuminuria, secondary anemia and no other evidences of renal insufficiency. This, of course, is good advice and it has resulted in the recognition of many cases of Bence-Jones proteinuria and multiple myeloma in which the diagnosis otherwise would have been missed. But too much emphasis has been placed on the "absence of other evidences of renal insufficiency," and as a result Bence-Jones proteinuria and myeloma have not been sufficiently considered in cases in which these "other evidences" have been present. In too many instances renal insufficiency with proteinuria and anemia have been diagnosed as nephritis of some sort, and thought has not been given to the possibility of Bence-Jones proteinuria. It is only when the frequent association of the proteinuria and renal insufficiency is appreciated, and when the characteristic and unusual clinical picture is observed, that the large proportion of these cases can be correctly diagnosed.

In several of the cases reported the diagnosis was made, even without appreciation of the frequent association of proteinuria and nephritis, because of the unusual clinical picture and the difficulty in explaining this picture by classifying it as any of the usual types of nephritis. Most of these patients are elderly people in whom renal insufficiency is usually explainable on the basis of a chronic pyelonephritis or by arteriosclerotic changes in the kidneys. However, the association of marked proteinuria and marked anemia, which is usual in Bence-Jones proteinuria is unusual in either chronic pyelonephritis or renal arteriosclerosis. The question of possible glomerulonephritis arises. Here again, the age of the patient, the absence of edema, of retinitis, and in many cases the absence of hematuria and hypertension as well is very unusual. Lastly, the frequent occurrence of marked anemia distinguishes these cases from the ordinary examples of chronic nephrosis. In cases in which the physician meets with so many difficulties in the endeavor to classify the so-called nephritis correctly, he should think of the possibility of Bence-Jones proteinuria.

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4 Wilson, D. W. A Spontaneous Crystallization of a Bence-Jones Protein, *J. Biol. Chem.* **56** 203, 1923.

This process of reasoning is especially applicable in cases without hypertension, but is sound even when hypertension is present. This is borne out very well in case 7, in which there was definite renal insufficiency, with a blood urea of 132 mg per hundred cubic centimeters and an excretion of phenolsulphonphthalein of 10 per cent. The age of the patient, the absence of edema, of hematuria or of retinitis, and the presence of marked hypertension, suggested that the renal insufficiency was on a vascular basis, but the anemia was somewhat out of proportion to what could be expected in such cases. Likewise, the "albuminuria" was profuse. It was, therefore, thought advisable to examine the urine for Bence-Jones protein and the correct diagnosis was thus made.

We do not wish to speak dogmatically regarding the cause of the renal insufficiency in these cases of Bence-Jones proteinuria because we were unable to corroborate our opinion by an examination of the kidneys in any of them. We believe, however, that a discussion as to the possible and probable causes is permissible, since it is based on a relatively large series of our own cases, with carefully controlled clinical and laboratory data, and on the clinical and pathologic descriptions that are scattered throughout the literature. Certain authors are of the opinion that chronic nephritis, with retention of nitrogen and low blood pressure, is typical of multiple myeloma and Bence-Jones proteinuria. Others believe that the chronic hypertensive type of nephritis, with retention of nitrogen, is the usual type. Our cases would seem to bear out the former idea, that the usual clinical picture is that of renal insufficiency, with little or no hypertension (ten of thirteen cases). Pyelonephritis produces this type of renal picture and apparently explains some of the cases reported in the literature, as, for example, in figure 12, published by Geschickter and Copeland in illustration of their case 7. Pyelonephritis probably is an important factor in the production of the insufficiency in several of our cases, cases 1, 3 and 9, however, it does not account for the renal insufficiency in most of them.

Thannhauser and Krauss<sup>5</sup> reported a case of multiple myeloma with Bence-Jones proteinuria and renal insufficiency of the type found in nephrosis with an exceptionally complete description of the renal lesion from both the clinical and the pathologic standpoints. The pathologic-anatomic description of the kidneys in their case can be summed up by saying that there were found small, white, smooth kidneys in which microscopic examination showed evidences of diffuse, high-grade,

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5 Thannhauser, S J, and Krauss, E. Ueber eine degenerative Erkrankung der Harnkanalchen (Nephrose) bei Bence-Jonescher Albuminurie mit Nierenschwund (kleine, glatte, weisse Niere), *Deutsches Arch f klin Med* **133** 183, 1920

degenerative change in the tubular epithelium, whereas the glomeruli were only slightly involved, the so-called nephrotic contracted kidney.

This description materially strengthens our belief that most of the renal insufficiency occurring in Bence-Jones proteinuria is the result of chronic tubular destruction with subsequent fibrosis. We believe this to be true of most of the cases reported in the literature as well as of our own series.

The cases which occur with arteriosclerosis and hypertension, we believe are the result of arteriosclerosis alone, or of arteriosclerosis combined with pyelonephritis or nephrosis. It is entirely possible that the renal injury and the profound proteinuria may contribute to the increase of the arteriosclerotic factors which are already playing a part in many of these elderly patients. The occurrence of true glomerulonephritis apparently is rare, but that it does occur is suggested by a few cases, for example, by Geschickter and Copeland's case 1. The amyloid reaction also has been reported in the kidneys in several cases.

Longcope<sup>6</sup> and others<sup>7</sup> have emphasized the importance of foreign proteins in producing renal irritation and nephritis. Geschickter and Copeland reported that Stokvis claimed to have induced nephritis in dogs by the injection of the Bence-Jones protein. The majority of investigators have found that normal dogs can utilize or catabolize moderate amounts of Bence-Jones protein, but the excess beyond a certain limit is excreted in an unchanged condition. Jacobson<sup>8</sup> considered that renal insufficiency led to retention of Bence-Jones protein in the blood stream. Decastello,<sup>9</sup> on the other hand, went so far as to suggest that the Bence-Jones protein is retained by the normal kidney and that a certain degree of nephritis is necessary to permit its appearance in the urine. These observations as well as those of Krauss<sup>10</sup> indicate that the nephritic kidney may be somewhat more permeable for Bence-Jones protein than the normal kidney. However, it has been shown by the observations of Taylor, Miller and Sweet<sup>11</sup>, Walters<sup>2</sup> and others

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6 Longcope, W. Production of Experimental Nephritis by Repeated Protein Intoxication, *J. Exper. Med.* **17** 679, 1913.

7 Thomas, W. A., Sehlegel, K. W., and Andrews, Edmund. Urinary Proteins Not Originating in Blood, *Arch. Int. Med.* **41** 445 (March) 1928.

8 Jacobson, V. C. A Case of Multiple Myelomata with Chronic Nephritis Showing Bence-Jones Protein in Urine and Blood Serum, *J. Urol.* **1** 167, 1917.

9 Decastello, Alfred. Beiträge zur Kenntniss der Bence-Joneschen Albuminurie, *Ztschr. f. klin. Med.* **67** 319, 1909, Weitere Beobachtungen über Bence-Jonesche Albuminurie bei Leukämie, *Wein. Arch. f. inn. Med.* **1** 335, 1920.

10 Krauss, Erich. Studien zur Bence-Joneschen Albuminurie, *Deutsches Arch. f. klin. Med.* **137** 257, 1921.

11 Taylor, A. E., Miller, C. W., and Sweet, J. E. Studies in Bence-Jones Proteinuria. II, *J. Biol. Chem.* **29** 425, 1917.

that if a sufficient quantity of Bence-Jones protein is administered it will pass through the normal kidney. We also have observed several cases of prolonged Bence-Jones proteinuria in which renal disease could not be demonstrated even by close scrutiny. In one instance, case 14, the Bence-Jones proteinuria apparently had been present for three years. D'Allocco and others have reported the presence of Bence-Jones protein in the blood, and have considered it to be a renal mutant and so responsible for the development of a type of nephritis, which, however, did not show the clinical characteristics of true chronic interstitial nephritis. Later writers, such as Bewley,<sup>12</sup> recognized the association, but they insisted even more strongly that the condition is not true nephritis, rather it is to be ascribed to renal irritation produced by the passage of Bence-Jones protein through the kidney. The interesting observations of Thannhauser and Krauss already have been noted.

Krauss also made repeated injections of Bence-Jones protein intravenously into four rabbits and produced changes in the kidneys which he interpreted as nephrosis. He emphasized the similarity, both functionally and pathologically, between the kidneys in some of these rabbits and the kidneys in the patient with Bence-Jones proteinuria previously reported by Thannhauser and Krauss. He expressed the belief that the nephrosis is caused by a general toxic reaction as well as by excretion of large amounts of this protein substance through the kidney.

Perlzweig, Delue and Geschickter,<sup>13</sup> in addition, reported a case of multiple myeloma with marked hyperproteinemia, in which only traces of Bence-Jones protein were present in the serum.

Our own observations on the serum proteins and on the occurrence of Bence-Jones protein in the blood in such cases and, as well, those reported in the literature are summarized in table 2. Hyperproteinemia is not a constant characteristic, for it was present in only four of the eleven reported cases in which the serum proteins were determined. This hyperproteinemia apparently is due to increase in the euglobulin. Similar changes have been observed in immunization experiments and in the production of diphtheria antitoxin in horses. Perlzweig, Delue and Geschickter, therefore, considered that the hyperproteinemia in these cases may be interpreted as a systemic response to protracted intoxication with a foreign protein. This question cannot be answered definitely without further knowledge.

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12 Bewley, Geoffrey. Bence-Jones Proteinuria, *Irish J. M. Sc.*, 1927, p. 321.

13 Perlzweig, W. A., Delue, Georges, and Geschickter, Charles. Hyperproteinemia Associated with Multiple Myelomas. Report of an Unusual Case, *J. A. M. A.* 90:755 (March 10) 1928.

regarding the source and origin of the serum proteins, but in view of the extensive disturbance of the bone marrow that is assumed to be responsible for the formation of the Bence-Jones protein, a similar cause may well be postulated for disturbances in the character of the serum proteins

Jacobson reported the presence of 7.86 per cent of Bence-Jones protein in the blood serum. We used this method in case 8. An abundant precipitate was obtained, but the Bence-Jones protein was contaminated by the presence of considerable amounts of globulin. Attempts at further separation led to considerable loss. Accurate separation of the Bence-Jones and serum proteins is not possible by the use of present day methods. As a result, we believe that the various figures previously reported with regard to the amount of Bence-Jones protein in the blood are only approximate at best. However, qualitative studies showing its presence or absence are more easily carried out.

Table 2 shows that Bence-Jones proteinuria frequently but not necessarily accompanies Bence-Jones proteinuria. Bence-Jones proteinuria was present in fifteen and absent in five of the cases reported. Some degree of renal insufficiency was present in most of the cases in which Bence-Jones protein was present in the blood. Here again the relationship was not absolute, for there are cases not only of Bence-Jones proteinuria but also of proteinemia without demonstrable renal insufficiency, and cases of renal insufficiency occurred in which the Bence-Jones protein could not be demonstrated in the blood.

It is evident, therefore, that the study of the blood proteins, with especial reference to the presence or absence of the Bence-Jones protein, has not served to establish a truly constant relationship between the changes in the latter and those in the kidneys.

#### SUMMARY

The frequent association of renal insufficiency and Bence-Jones proteinuria is emphasized. The usual clinical picture is that of marked proteinuria, rather marked secondary anemia, nitrogen retention, delayed excretion of phenolsulphonphthalein, little or no edema and little or no hematuria, hypertension or retinitis. This picture seems usually to be the result of destructive processes in the kidney, either tubular destruction with subsequent fibrosis or pyelonephritis. Associated arteriosclerosis and hypertension may occur in some cases. The occurrence of true glomerulonephritis is rare. The urine should be examined for Bence-Jones proteinuria in all patients presenting the group of symptoms just mentioned and in all cases in which profound proteinuria exists, especially when associated with anemia. In this way, many cases of Bence-Jones proteinuria will be recognized which,

at the present time, are being overlooked. This in turn will provide more data for the study of the nature of the renal insufficiency.

The presence of Bence-Jones protein in the blood has been demonstrated in approximately 70 per cent of the cases in which examination, as suggested, has been reported. Hyperproteinemia is present in a smaller proportion of cases. There apparently was no constant relationship between this condition and the presence or absence of demonstrable renal insufficiency.



# RETICULOCYTOSIS PRODUCED BY LIVER EXTRACT

TWO, THREE AND FOUR HOUR INTERVAL OBSERVATIONS<sup>1</sup>

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AND

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During the past year and a half we have studied the response of patients with pernicious anemia to an aqueous extract of liver. This work has been conducted in conjunction with observers in three other clinics, so that a comparison could be made with the response to whole liver and to other liver extracts, to the end that an unbiased evaluation of its clinical worth might be established. The report of this work covers a study of forty-five patients with a macrocytic type of anemia.<sup>1</sup> From a study of these patients, we conclude that liver extract E 29<sup>2</sup> produces results in every way similar to those which occur from the feeding of whole liver, except that the response is more prompt and rapid because the effective material from larger amounts of liver can be administered by this method.

Minot<sup>3</sup> and his co-workers have established the fact that the most reliable criterion for evaluating the potency of a liver fraction is the response of hyperplastic bone-marrow to the effective substance, as evidenced by the number of reticulocytes appearing in the circulating blood. They suggested that the number of newly formed erythrocytes retaining a reticulum stained with brilliant cresyl blue roughly indicates, on the one hand, the degree of bone-marrow hyperplasia, and on the other, the effective

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<sup>\*</sup> Submitted for publication, May 17, 1929

<sup>1</sup> From the Department of Medicine, Medical College of Virginia

1 Porter, William B., Williams, J. Powell, Forbes, J. C., and Irving, H. Aqueous Extract of Liver, Its Development and Use in the Treatment of Pernicious Anemia, *J. A. M. A.* **93** 176 (July 20) 1929

2 Liver extract E 29 has been developed by the Department of Medicine and Biochemistry of the Medical College of Virginia, in collaboration with the Valentine Meat Juice Company, Richmond, Va.

3 Minot, G. R., and Murphy, W. P. Treatment of Pernicious Anemia by a Special Diet, *J. A. M. A.* **87** 470 (Aug 14) 1926. Cohn, E. J., Minot, G. R., Fulton, J. E., Ulrichs, H. F., Sargent, F. C., Weare, J. H., and Murphy, W. P. The Nature of the Material in Liver Effective in Pernicious Anemia, *J. Biol. Chem.* **74** 69, 1927. Minot, G. R., Cohn, E. J., Murphy, W. P., and Lawson, H. A. The Treatment of Pernicious Anemia with Liver Extract. Effect upon the Production of Immature and Mature Red Blood Corpuscles, *Am. J. M. Sc.* **175** 599, 1928. Minot, G. R., Murphy, W. P., and Stetson, R. P. The Response of the Reticulocytes to Liver Therapy. Particularly in Pernicious Anemia, *Am. J. M. Sc.* **175** 581, 1928.

tive concentration of the substance producing erythrogenesis. The same observers noted, however, that "when maximum amounts are taken daily the number of reticulocytes at the peak of their rise per gram of liver fed is nowhere nearly as constant as when smaller amounts are fed." They also noted variation in the magnitude of the reticulocyte response of different patients given the same amount of active principle, even when they have the same erythrocyte level. They concluded that "this variability is probably to be attributed to the state of the bone marrow."

Using daily counts as a guide to bone-marrow response, we early noted that there was a marked variation in the percentage of reticulo-

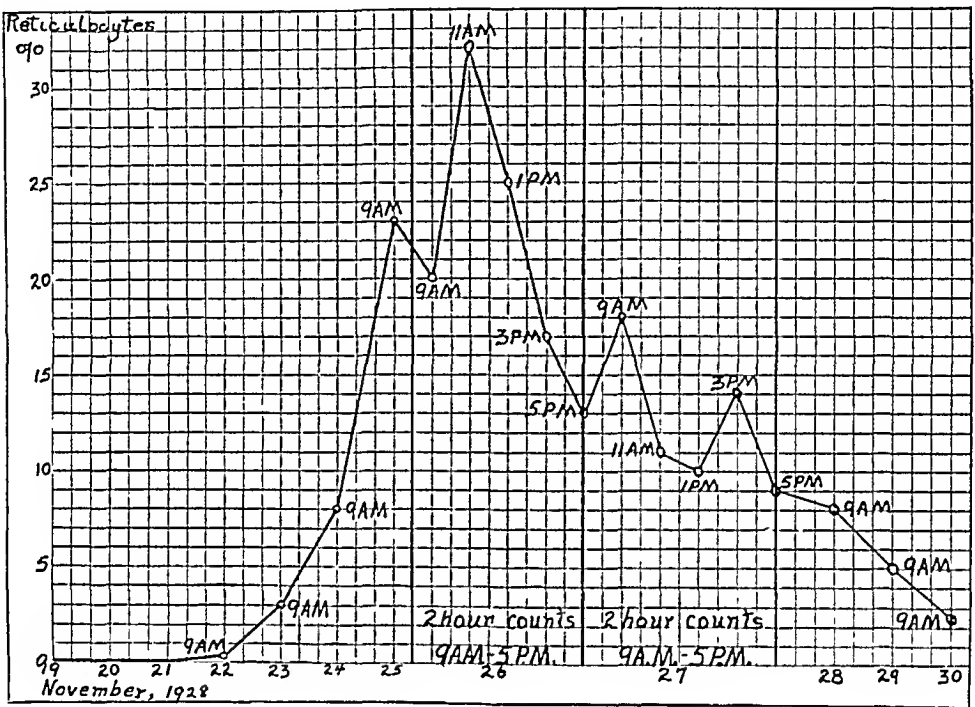


Chart 1—Curve showing the percentage of reticulocytes at intervals of two hours following the administration of 30 cc of liver extract E 29, three times a day beginning November 21. The Minot-Murphy diet without liver was used. The patient (case 1016), aged 66, had a hemoglobin of 35 per cent, an erythrocyte count of 1,360,000 and a leukocyte count of 3,200.

cytes released in different patients with the same degree of anemia and in whom the percentage of increase in hemoglobin and erythrocytes was consistent and practically identical. This showed that while the material was manifestly potent there remained a paradoxical reaction not subject to explanation, i. e., a variable and at times a low percentage of reticulocyte response but a rapid increase in hemoglobin and erythrocytes, suggesting that the effective material found in liver operates in a twofold manner. The promotion of erythrogenesis in flooding the circulation with immature red cells represents the primary effect, whereas the rapid



and complete development of reticulocytes into mature red cells resulting from the maintenance in the circulating blood of a high concentration of the effective material is the phase that might prove misleading in the reckoning of reticulocytosis

Anticipating this possible source of error, we studied a series of patients with erythrocyte counts of less than 1,500,000 per cubic millimeter who were given 30 cc of liver extract E 29 three times a day, this amount having proved to be adequate to produce a prompt and maximum erythrogenesis in pernicious anemia. Counts were made in group 1 at intervals of two hours, in group 2, at intervals of three hours, while in group 3, they were made only twice a day, at 8 a m and 4 30 p m. Three representative curves are reproduced in charts 1, 2 and 3.

Among the many interesting phases suggested by these charts of bone-marrow physiology functioning under the influence of the substance supplied by feeding liver, the rapid variation in the percentage of reticulocytes in a few hours is most striking, and the occurrence of several peaks on different days is in contrast to previously reported studies on this phase of bone-marrow physiology. Broadly speaking, the charts represent not only the degree of bone-marrow hyperplasia, but also a play between the release of reticulocytes and the complete maturation of the reticulated erythrocytes in the circulation into adult red cells by the same effective substance concentrated in the blood plasma.

#### CONCLUSIONS

These observations suggest that if a liver fraction is potent and is administered in adequate amounts, the maximum number of reticulocytes in the circulating blood may be present for a brief period. The total number of reticulocytes released in a given case is dependent on the volume of hyperplastic bone-marrow, however, the percentage of reticulocytes may vary widely, dependent on the frequency of observations. Obviously this is a factor of major importance if one is to use the percentage of reticulocytes as an index to potency and in establishing therapeutic dosage.

# THE HEMOGLOBIN PERCENTAGE AND THE RED BLOOD CELL COUNT IN BRIGHT'S DISEASE, MYOCARDIAL INSUFFICIENCY AND HYPERTENSION \*

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## Introduction

### Material Studied

#### Bright's Disease

### Analysis of Average Results

#### Myocardial Insufficiency

#### Hypertension

### Analysis of Individual Cases

#### Acute Nephritis

##### Effect of Hematuria

##### Effect of Etiologic Factor

##### Effect of Complications

#### Chronic Diffuse Nephritis

##### Effect of Infections (Granuloma)

##### Effect of Albuminuria and Edema

#### Hypertension with Varying Degrees of Renal Insufficiency

##### Myocardial Insufficiency

##### Cerebral Lesions

### Color Index (Nature of the Anemia)

#### Renal Insufficiency

#### Myocardial Insufficiency

#### Cerebral Lesions

### The Effect of Anemia on Kidney Function

### Conclusions

## INTRODUCTION

The problem of anemia in nephritis has received comparatively little attention, though its clinical incidence is high. This is in a measure due to the fact that the conception of nephritis as a constitutional disease, not exclusively related to renal pathology and symptomatology, is only slowly gaining clinical recognition. The remarkable studies of Volhard and Fahr and other pathologists and physicians, while serving to elucidate many problems with regard to renal symptomatology and postmortem observations, have detracted from the broader view of nephritis as a disease involving both renal and extra-renal factors. In the classic lecture

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of Theodore C Janeway,<sup>1</sup> given before the Harvey Society in 1913, the remark was made that the three most important aspects of the problem of nephritis are edema, uremia and hypertension. To these Mosenthal<sup>2</sup> added a fourth factor, renal insufficiency, and for some years it has been his practice, in presenting nephritis to postgraduate students, also to include anemia.

Much of the work on anemia in this disease, preceding 1913 and 1915, is contradictory chiefly because it is only since these years that tests for kidney function have been available. In 1922 and 1923, Brown and Roth<sup>3</sup> concluded, from a study of 187 cases of chronic glomerular nephritis, that most patients with this condition were subject to an anemia which was directly proportional to the increase of creatinine in the blood, they also called attention to the prognostic significance of their data.

It is the object in this paper to show that anemia is associated with and closely parallels the degree of impairment of renal function, that this relationship holds true for renal insufficiency whatever its cause, that it applies whether the kidney lesion is acute or chronic, glomerular or diffuse, or a primary or secondary contraction. Certain modifications of the view proposed in the preceding sentence must be made for those stages of impairment of kidney function associated with congestive myocardial insufficiency, and for the cerebral manifestations associated with hypertension. But in these instances too, types of blood count are found, distinctive of each, which so far from vitiating the effect of the general conclusion, in fact serve as aids in estimating the relative importance of the kidney, heart and brain in the combination of signs and symptoms which make up the different types and stages of "cardiovascular renal" disease.

#### MATERIAL STUDIED

The 300 cases comprised in this study were taken from the medical histories recorded by Mosenthal on the service of the late Theodore C Janeway, at the Johns Hopkins Hospital from 1914 to 1918, from private practice and from the medical service at the New York Post-Graduate Medical School and Hospital. This selection has the advantage of obviating the factor of individual technic in blood counting and lends value to the consistency of data obtained from various sources. The red blood cell counts were made in the usual manner. The hemoglobin determinations were made by the Sahli method in about 75 per cent

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1 Janeway, T. C. Nephritic Hypertension (Harvey Lecture), *Am J M Sc* **145** 625 (May) 1913.

2 Mosenthal, H. O. *Metabolism in Nephritis, Endocrinology and Metabolism*, New York, D. Appleton & Company, 1922, vol 4, p 312.

3 Brown, G. E., and Roth, G. M. The Anemia of Chronic Nephritis, *Arch Int Med* **30** 817 (Dec) 1922, The Prognostic Value of Anemia in Nephritis, *J A M A* **81** 1948 (Dec 8) 1923.

of the cases, and by the Dare hemoglobinometer in the remaining 25 per cent. These were checked occasionally by the chemical determination of the hemoglobin and by the Newcomer method.

Twenty-five cases of acute nephritis, 111 cases of chronic diffuse nephritis and 132 cases of hypertension are presented. Of these, sixty-eight cases showed cardiac decompensation, and in twelve cases of hypertension, cerebral lesions (and some impairment of kidney function) played the chief rôle in the clinical picture. For purposes of comparison and control, there were added eighteen "pure" cardiac cases, five "surgical" cases, five of polycythemia and four with secondary anemia.

For the majority of cases information was obtained as to the hemoglobin, red blood cells, color index, urinalysis, two hour renal function test, urea nitrogen in the blood, phenolsulphonphthalein excretion and blood pressure. In a few cases, in which the circumstances under which the patients were studied did not permit of so complete an analysis, sufficient clinical, laboratory and postmortem data were obtained to justify the grouping of these cases as charted in the tables. In many cases additional studies were made on the blood chemistry, Ambard's constant, etc., which have been of aid in determining the classification employed in the tables given in this paper.

The criteria according to which these cases were grouped as to the degree of impairment of renal function are based on the standards suggested by Mosenthal and Lewis,<sup>4</sup> and classified as none, slight, moderate, marked or maximal.

An analysis of average results is given in table 1.

*Bright's Disease*—In Bright's disease, the severity of the anemia and the degree of renal insufficiency run a parallel course. In the cases of acute nephritis, a distinct diminution of the hemoglobin and red cell figures parallels the increasing impairment of kidney function. Thus, in the group of patients with little if any impairment, the hemoglobin averages 90 per cent and the red cells 4,887,000 as contrasted with 77 per cent and 4,606,000 for the patients with moderate impairment and 69 per cent and 3,869,000 for those with marked to maximal impairment.

The corresponding degrees of impaired renal function in chronic diffuse nephritis show similar degrees of anemia. 87 per cent hemoglobin with 4,759,000 red cells in the cases exhibiting little if any renal insufficiency. 69 per cent and 4,083,000 in the group with moderate impairment and 54 per cent and 2,944,000 in those with marked or maximal renal insufficiency.

It is significant that the renal insufficiency accompanying hypertension (where infection plays no known part in connection with the renal

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4 Mosenthal, H. O., and Lewis, D. S. A Comparative Study of Tests for Renal Function, J. A. M. A. 67:933 (Sept. 23) 1916.

lesion) is associated with an anemia of varying degrees which, as in acute and chronic nephritis, parallels the extent of impairment of kidney function. The average figures for the hypertensive cases are 88 per cent hemoglobin with 4,848,000 red cells when little if any impairment was found, 81 per cent with 4,763,000 red cells in the patients with moderate involvement and 65 per cent with 3,775,000 red cells when the kidneys showed marked or maximal insufficiency.

## ANALYSIS OF AVERAGE RESULTS

TABLE 1—*Average Hemoglobin, Red Blood Cells and Color Index in Relation to Diagnosis and Renal Function*

Diagnosis	Average			Data on Individual Cases Given in Table No.	Number of Cases
	Hemoglobin, per Cent	Red Blood Cells Millions per C. Mm.	Color Index		
Acute Nephritis					
No or slight impairment	91	1,887	0.93	2	10
Moderate	77	1,606	0.83	2	5
Marked and maximal	69	3,869	0.90	2	10
Chronic Diffuse Nephritis					
No or slight impairment	87	1,759	0.92	3	21
Moderate	69	1,083	0.86	1	25
Marked and maximal	54	2,911	0.93	5 and 6	10
Myocardial Insufficiency with Diffuse Nephritis					
No or slight impairment	77	1,863	0.78	3	9
Moderate	81	1,735	0.89	1	10
Marked and maximal	72	1,593	0.83	5 and 6	8
Hypertension					
No or slight impairment	88	1,818	0.91	7 and 8	36
Moderate	81	1,763	0.86	9	16
Marked and maximal	65	3,775	0.87	10 and 11	27
Myocardial Insufficiency with Hypertension					
No or slight impairment	77	1,881	0.80	7 and 8	12
Moderate	80	5,011	0.80	9	16
Marked and maximal	72	1,230	0.85	10 and 11	13
Cases of Hypertension with Evidence of Cerebral Pathology					
No or slight impairment	91	5,179	0.89	7 and 8	7
Moderate and marked	96	5,392	0.90	9 and 10	5

The relation of kidney function to anemia is borne out by a study of patients in whom renal insufficiency followed polycystic degeneration of the kidneys, or nephrectomy.

In one case of polycystic kidney, with moderately impaired renal function, the anemia was correspondingly slight, with 80 per cent hemoglobin and 4,256,000 red blood cells. Two cases which exhibited maximal renal insufficiency showed severe anemia, with hemoglobin percentages of 44 and 55 and with erythrocyte counts of 2,728,000 and 3,900,000, respectively.

The patient in case 272, with one kidney removed but with no impairment of kidney function, showed a hemoglobin of 80 per cent on one occasion and 90 per cent on another. On the other hand, in case 275, in which removal of one kidney was followed by maximal renal insufficiency, the anemia was marked, the hemoglobin being 45 and 56 per cent and



the red cells numbering 2,500,000 and 3,882,000 on two counts taken at an interval of some months

These observations confirm the general statement previously made that the anemia parallels the renal dysfunction no matter what the cause of the latter may be and varies in the clinical types of nephritis only so far as these diseases differ in the frequency and degree to which they develop renal insufficiency. This may explain the diversity of opinion embodied in the discussions of anemia in nephritis in texts written prior to the days of adequate tests for renal function. It may be supposed that the authors who noted little if any anemia in chronic diffuse nephritis were probably dealing with cases in which the patients showed slight or no renal insufficiency, whereas those reporting marked and severe anemia were presumably observing patients with marked and maximal impairment of function.

*Myocardial Insufficiency*—Under the heading of myocardial insufficiency in table 1 are shown the results in cases of cardiac decompensation occurring in patients with chronic diffuse nephritis and in cases of hypertension. These exhibited certain characteristics which distinguish them from cases in which there is no decompensation. Analysis discloses that the hemoglobin is usually relatively more decreased than are the red cells. In fact, the red cell count is but little or not at all diminished, even in cases with maximal renal insufficiency—a feature which is in striking contrast with the conditions already mentioned in uncomplicated nephritis. The color indexes in these cases thus tend to be lower than those occurring in the cases of Bright's disease.

The counts in the cases of myocardial insufficiency accompanying chronic diffuse nephritis are as follows: with no or slight impairment of renal function, the hemoglobin averaged 75 per cent and the red cells 4,863,000. When the function was moderately impaired, the average hemoglobin was 84 per cent and the red cells 4,735,000, with marked and maximal renal insufficiency the hemoglobin averaged 72 per cent and the red cells 4,393,000.

The statistics for myocardial insufficiency associated with hypertension are essentially the same as for the group just cited. In other words it would appear that myocardial insufficiency, like renal insufficiency, presents certain characteristics independent of its cause. When the "hypertensive myocardial insufficiency" occurred with little if any renal insufficiency, the average figure for the hemoglobin percentage was 77, and for the red cells 4,881,000, patients with accompanying moderate renal insufficiency have hemoglobin and red cell values of 80 per cent and 5,044,000, respectively. At the stage of marked and maximal renal insufficiency the average figure for hemoglobin is 72 per cent and the red cells number 4,250,000.

As a control, eighteen cases of heart disease, with decompensation not associated with nephritis of any type, were studied as to renal function and blood count. These cases manifested the same peculiarities as to a relatively high number of red cells compared to the percentage of hemoglobin and the impairment of kidney function. Here too, the color index was low as compared with the cases of Bright's disease.

An anomalous observation presents itself in that the blood counts in the cases of myocardial insufficiency associated with moderate renal insufficiency are higher than the counts in cases associated with normal kidney function or slight impairment. At present, only the following conjectures may be put forth in attempted explanation. These were patients in whom heart disease of the congestive type with decompensation was noted during the course of diffuse nephritis and primary contraction of varying degrees of severity. It must be borne in mind, however, that the chronic passive congestion which these patients show, and which can be detected by the two hour test for renal function (Mosenthal<sup>5</sup>), is itself a factor in producing at least part of the renal insufficiency. This was borne out by the impaired renal function demonstrated in the "puke" cardiac cases used as controls. An increased congestion would logically cause more impairment of kidney function than the lesser degree of stasis. That the cases of congestive cardiac failure with maximal renal insufficiency have the lowest hemoglobin and red cells might be interpreted as indicating that at this stage the anemia consequent on the marked renal lesion plays a greater part in the picture. To approach the matter from another angle, it would seem that the congestive heart failure disguises a true anemia which would, in the absence of the peripheral stasis (which accounts for the high blood count), parallel the kidney function impairment as it does in uncomplicated Bright's disease. When the renal insufficiency is extreme, the congestion cannot affect the marked anemia to nearly so great an extent as it does when kidney function is moderately or slightly impaired.

This is illustrated by case 286, in which there was chronic passive congestion, but death occurred from uremia. The blood count was 39 per cent of hemoglobin with 2,160,000 red cells and a color index of 0.92.

The failure of anemia to parallel the degree of renal dysfunction points to myocardial insufficiency as a cause of the impaired kidney function, the edema, the albuminuria, etc. It is precisely in the congestive type of myocardial insufficiency that impaired renal function is most

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5 Mosenthal, H. O. Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen and the Specific Gravity of the Urine, *Arch Int Med* 16 733 (Nov.) 1915

prone to ensue, as Stewart and McIntosh<sup>6</sup> of the Rockefeller Institute have shown in their recent study of kidney function in patients with chronic cardiac diseases

*Hypertension*—The cases of hypertension show three types of blood count, depending on whether impairment of renal function, myocardial insufficiency or cerebral involvement predominates. It is generally appreciated that the kidney, the heart and the brain are the principal, if not the sole important, sites for secondary involvement in essential hypertension (Janeway<sup>7</sup>)

The bearing of the blood count in hypertension with respect to renal insufficiency and to myocardial insufficiency has been previously discussed. It has been demonstrated that these conditions of functional impairment, secondary to a persistently elevated blood pressure, induce changes in the blood count identical with those resulting from renal or myocardial insufficiency of any origin.

When the cases of hypertension are tabulated according to the degree in which they exhibit impaired renal function, a group of cases is found with high normal or polycythemic blood counts though some of the patients have moderate, and in one case, marked renal insufficiency. On closer study, the interesting fact is revealed that these patients have a common diagnosis, i.e., some manifestations of cerebral disease, as for example hemiplegia and focal occlusion of cerebral blood vessels. Table 1 gives the data with respect to such cases. With little if any renal insufficiency the average hemoglobin was 91 per cent and the red cells 5,179,000, with moderate and marked impairment of kidney function a hemoglobin average of 96 per cent and a red cell count of 5,392,000 are recorded. Here, as in the cases of myocardial insufficiency, it appears anomalous that the higher blood count should be found in the cases with lower kidney function. The same principle applies, however, since the polycythemia causes some renal impairment it is natural to expect that the more marked the polycythemia, the more damage will be done to the kidney. At any rate, here again, an inconsistency between the state of kidney function and anemia is a means whereby, in some cases, a clue to diagnosis is obtained pointing to an organ other than the kidney as the chief cause of the symptomatology.

The importance of this relationship in estimating whether the patient is comatose from cerebral damage or from uremia, and its prognostic value in less advanced cases, is apparent. Lamson<sup>8</sup> stated that the urine

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6 Stewart, J. H., and McIntosh, J. F. The Function of the Kidneys in Patients Suffering from Chronic Cardiac Disease Without Signs of Heart Failure, *J. Clin. Investigation* 6: 325 (Oct. 20) 1928.

7 Janeway, T. C. A Clinical Study of Hypertensive Cardiovascular Disease, *Arch. Int. Med.* 12: 755 (Dec.) 1913.

8 Lamson, P. D. Polycythemia, in Nelson. Loose Leaf Medicine, New York, Thomas Nelson & Sons, 1920, vol. 4, p. 92.

in polycythemia may contain a trace of albumin. Gaisbock and Hess and Eppinger,<sup>9</sup> quoted by Lamson<sup>8</sup> and Piney<sup>9</sup> demonstrated that these cases usually show signs of kidney disturbance, although in some this may be slight. Albuminuria and nephritis of slight degree are common. The blood pressure is often raised. Gulland and Goodall<sup>10</sup> mentioned the increased blood pressure in polycythemia and, like Eppinger, pointed out that this is apparently most marked in the cases showing no enlargement of the spleen clinically. The urine is usually abundant and may be clear, but often contains albumin and casts.

These quotations from the literature, as well as the fact that in the series now being reported the cases (except controls added for comparison) are chosen from a group studied for renal function because of some indications pointing to the kidney, show how the problem of differential diagnosis may arise and wherein the blood count may be of value. That the classification of these patients into a so-called "brain" group is justifiable may be gathered from the lesions diagnosed in these cases, as given in tables 7 to 11, and from the following citations from the literature. Gulland and Goodall<sup>10</sup> stated that "These cases show cyanosis, thrombosis, hemorrhage or other local circulatory disorders.

The end is usually associated with an exacerbation of cyanosis or a vascular brain lesion or an intercurrent affection." Gaisbock, quoted by Piney,<sup>9</sup> stated that apoplexy occurs with great frequency in this form of polycythemia (i.e., associated with hypertension and no enlargement of the spleen), while it is rare in the usual type. He recorded that the disease may develop in persons who had previously had an apoplectic seizure.

This is the attitude taken by Piney,<sup>9</sup> Eppinger and others.

The particular form of erythremia described by Gaisbock deserves separate description, although many writers are not at all satisfied that it must be put in a special sub-group.

Eppinger suggests that the so-called "polycythemia hypertonica" represents the effects of erythremia in persons with renal arteriosclerosis. The absence of notable splenic enlargement can scarcely be regarded as a definite differential feature because both Senator and Stern have described ordinary cases of erythremia in which splenic enlargement was found only at autopsy.

In Kocher's<sup>11</sup> analysis of the four stages of increased intracranial pressure experimentally produced, cyanosis figures prominently as part of the picture in the second and third stages.

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9 Piney, A. Recent Advances in Hematology, Philadelphia, P. Blakiston's Son & Company, 1927.

10 Gulland, G. L., and Goodall, A. The Blood, New York, E. B. Treat & Company, 1922.

11 Kocher's Experiments, described in "Surgery of the Brain," Harvey Cushing, Keen's Surgery, Philadelphia, W. B. Saunders Company, 1919, vol. 3, p. 195.

## ANALYSIS OF INDIVIDUAL CASES

*Acute Nephritis*—Twenty-five cases of acute nephritis are analyzed in table 2. The general rule holds true that the blood count is reduced as kidney damage develops.

Certain exceptions occur which might properly have been omitted from the material studied, but it was felt that a more representative picture of all the factors influencing anemia would be obtained if no exclusions were made.

TABLE 2—*Acute Nephritis*\*

No	Blood Count				Urine			Blood Pressure	Edema	Comment
	Case No	per Cent	Hemo- globin, Mil- lions	Red Cells, Color Index	Albu- min	Red Blood Cells	Casts			
1	297	50	2 850	0 87	++++	++++	+++	132/ 80	+	Gross hematuria
2	243	90	4 816	0 93	Trace	Rare	Occ	176/ 86	0	
3	46	97	4 368	1 12	v f t	Few	0	117/ 85	0	
4	55	90	4 544	1 0	+	0	+	102/ 70	+	
5	53	90	6 120	0 73	+++	0	0	130/ 80	++	
6	217	85	4 768	0 9	+++	+++	+	110/ 64	+	Taking large amounts water Respiratory infec- tion
7	56	66	3 772	0 80	++	0	+	160/100	+	
8	61	95	5 972	0 8	+	Occ	+	148/ 90	+++	
9	87	92	4 736	0 97	Trace	0	0	125/ 95	0	
10	88	80			+++	+	+	150/100	0	
11	48	97	4 832	1 01	++	0	++	130/ 90		
12	51	72	4 832	0 75	++	+	+	220/120	++	
13	60	70	4 520	0 77	++++	Occ	+	165/ 80		
14	89	88			Trace	+	+	136/ 78		
15	90	70	4 040	0 87	+	+	+	115/ 75	+	
16	269	70	3 880	0 92	++	+	+	250/165		Convulsions, toxic uremia Healing stage of acute nephritis Catarrhal jaundice
17	47	100	4 636	1 08	Trace	Few	0	170/115		
18	49	85	3 424	1 3	Trace	Few	+	153/100	++	
19	52	34	2 018	0 85	++++	+	+	170/ 90	+	
20	53	70	4 120	0 85	++++	+	+	165/110	++	
21	57	43			++++	+++	++	155/120	+++	
22	59	78	4 572	0 86	++	+	+	120/ 78	0	
23	62	65	4 100	0 79	++++	+++	+++	140/ 90	+	Marked hematuria
24	50	65	4 352	0 75	++++	Few	+++	140/ 70	+	
25	54	65	3 920	0 83	+	+	+	163/100		

\* In uncomplicated cases, the anemia parallels the extent of impairment of renal function. Cases 1 to 5 no impairment of renal function, cases 6 to 10 slight, cases 11 to 15 moderate, cases 16 to 22 marked and cases 23 to 25 maximal impairment of function.

**Effect of Hematuria** The patient in case 297 (table 2), a girl, aged 14, showed a hemoglobin of 50 per cent and a red cell count of 2,850,000, although the renal function was normal. Marked macroscopic hematuria was manifest. This had no effect on the kidney function as tests showed, and must be given the same significance as hemorrhage from any source as a cause of the anemia. A review of the other cases in this table, as well as in tables 3 to 6 and 7 to 11, reveals the fact that the microscopic hematurias bear no constant relationship to the anemia. Although, for obvious reasons, the repeated losses of blood

may be a factor, equally severe grades of anemia occur in the cases that show no hematuria

**Effect of Etiologic Factor** Another disturbing element is that anemia in acute nephritis may be caused by the disease of which the nephritis is a result, for example, scarlet fever, streptococcus infection or malignant endocarditis. This factor must be carefully ruled out in interpreting the relation of anemia and kidney function, on the other hand, the presence of a moderate or marked anemia, though renal function is normal, might well serve to call attention to the existence of accompanying disease

**Effect of Complications** With respect to complications, the same point may be made. Thus, the patient in case 56 (table 2) showed a marked anemia (hemoglobin 66 per cent, red cells 3,772,000) although the kidney function was only slightly impaired. This is explained by the fact that the patient, a woman, aged 28, had an accompanying respiratory infection. In cases of this kind the physical signs and the presence of a leukocytosis may give clues as to the true nature of the anemia

*Chronic Diffuse Nephritis*—The data for 111 patients with chronic diffuse nephritis are presented in tables 3, 4, 5 and 6

In each group a number of cases occurred in which there were signs of cardiac insufficiency. These are indicated in each of the tables with a brief description of the condition

When congestion does not mask the anemia, it will be noted that the blood count parallels the degree of impairment of renal function. Most of the hemoglobin values range from 80 to 90 per cent with red cells from 4,250,000 to 5,500,000 when there was little or no impairment of kidney function (table 3), whereas the range was from 60 to 70 per cent with many red cell counts of approximately 3,500,000 when moderate renal insufficiency was present (table 4). When marked and maximal renal insufficiency supervened (tables 5 and 6), figures of 50 per cent, 40 per cent and 35 per cent for the hemoglobin are met with frequently and in fact dominate the picture. Accompanying these hemoglobin values are red cell figures which show counts of 3,000,000 and 2,500,000

Some of the exceptions to the general trend illustrate interesting points which must be ruled out before interpreting anemia in terms of renal function in chronic diffuse nephritis

Case 123 (table 3) is that of a woman, aged 38, in whom anemia was noted during the course of pregnancy. The red cells were much more reduced than was the hemoglobin, the color index was 1.11, and the question may be raised as to whether this was properly a case of chronic diffuse nephritis. The kidney function was normal. The anemia may represent the pernicious type of blood dyscrasia accompanying pregnancy and in no wise a subject for comparison with any renal disease

Case 6 (table 3) is one of nephrosis in a man, aged 20, who had recently been markedly edematous, though with the elimination of edema the renal function, at the time that the blood count was taken, was only slightly involved. It is reasonable to suppose that the hemoglobin of 65 per cent and the red cell count of 3,650,000 were the reflection of the more serious impairment of kidney function recently present. Adams

TABLE 3—*Chronic Diffuse Nephritis (No or Slight Impairment of Renal Function)*

No	Blood Count				Urine			Blood Pressure	Edema	Comment
	Case No	Hemo globin, per Cent	Red Cells, Mil lions	Color Index	Albu- min	Red Blood Cells	Casts			
1	233	90	5 408	0.83	++++	Occ	+	133/ 88	0	Albuminuria 4 yrs
2	263	82	4 000	1.02	++++	Occ	+	130/ 80	++	
3	4	80	5 560	0.72	+	0	0	120/ 80		
4	5	86	4 592	0.95	++++	0	+	122/ 78	+	
5	7	95	5 344	0.89	+++	Few	+	165/115	++	Slight oliguria
6	19	90	4 136	1.09	++++	0	+	140/ 90		Syphilis, malaria
7	21	93	4 832	1.02	++++	0	+	125/ 85	+	Eliminating edema
8	22	84	5 032	0.84	++++	+	+	210/130		
9	35	94	4 240	1.11	++	0	Occ	128/ 80	+++	Considerable edema and effusion
10	63	108	7 240	0.75	+ and 0	Occ	+	130/ 95	0	Polycythemia
11	42	100	5 334	0.94	++++	0	+	115/ 75		
12	179	85	4 830	0.98	Trace	0	0	132/ 98		
13	70	90	4 424	1.08	Trace	0	Occ	120/ 75	0	Epilepsy
14	78	95	5 600	0.84	++	Few	+	240/165		Slight nocturnal polyuria
15	123	80	3 644	1.11	Trace	0	0	180/120		Pregnancy, anemia
16	282	80	4 480	0.9	++++	Occ	+	116/ 57		
17	252	80	4 800	0.8	++++	+++	0	116/ 72		Pylitis
18	237	85	4 288	1.0	+	Occ	Occ	154/ 96		
19	260	83	4 696	0.9	++	0	0	214/136		Albuminuria for 10 years
20	287	80	4 326	0.93	++++	Occ	+	114/ 68	+	
21	6	65	3 650	0.90	++	0	+	140/100		Edema recently
22	10	80	5 488	0.74	Trace	0	+	180/ 95		Heart enlarged to right and left
23	34	78	4 320	0.90	++++	++	+	174/ 93	+	Pleural effusion
24	3	80	5 412	0.74	++	0	+	230/125	0	Enlarged heart
25	291	86	5 240	0.8	+	Rare	0	115/ 64		Hyperthyroidism
26	32	62	4 216	0.73	++++	0	+	210/115	+	Oliguria, pleural effusion
27	255	69	4 344	0.79	++++	Occ	0	180/110		Dilated aorta
28	245	80	5 536	0.72	++++	Many	0	159/ 98	0	Cardiac decompensation
29	34	78	4 320	0.90	++++	++	+	174/ 93	+	Pleural effusion
30	95	65	4 896	0.67	++++	0	+	183/112	+	Heart enlarged to right

\* Corresponding to the good kidney function, the blood counts are essentially normal. Items 22 to 30, inclusive, presented congestive myocardial failure.

and Brown<sup>12</sup> showed that the anemia is apt to persist, at least for a time, when renal function improves after marked impairment.

Cases 262, 33 and 40 (table 4) are grouped under the head of chronic diffuse nephritis with moderate impairment of kidney function. It is noteworthy that in each of these cases the red cells were unduly increased as compared to the hemoglobin, and, correspondingly, each of

TABLE 4—*Chronic Diffuse Nephritis (Moderate Impairment of Renal Function)*

No	Blood Count				Urine			Blood Pressure	Edema	Comment
	Case No	Hemo globin, per Cent	Red Cells, Mil-lions	Color Index	Albu-min	Red Blood Cells	Casts			
1	262	80	5 181	0 78	++++	0	+	157/105	+	Slight cyanosis
2	234	73	3 920	0 93	++	+	++	158/ 82	++	
3	235	70	4 984	0 7	++++	Occ	++	162/116	+	
4	251	62	3 600	0 86	++++	++	++	142/ 90	+	Oliguria
5	1	76	3 776	1 02	Trace	0	+	140/100	+	
6	12	75	3 864	0 98	Trace	+	+	200/110	+	
7	30	55	3 060	0 91	++++	+	+	140/ 85	+++	Tuberculous osteomyelitis
8	31	65	4 832	0 67	++	0	+	130/ 77	+	
9	33	63	4 384	0 73	++	Few	+	150/ 98	++	
10	38	65	3 832	0 87	0	0	0	130/ 80		Bichloride poisoning
11	40	68	5 000	0 68	+	0	+	170/130		
12	43	76	4 460	0 86	+	0	0	188/125	+	
13	66	75	4 280	0 89	v f t	0	+	115/ 65		Passive congestion
14	68	70	4 840	0 72	++++	++	+	115/ 95	+	
15	76	78	4 040	0 97	+++	0	+	175/115		
16	71	62	3 232	0 96	Trace	0	+	105/ 70	0	Duodenal ulcer
17	77	67	3 824	0 88	++	0	+	150/ 85	+	
18	23	73	3 932	0 93	++++	0	+	120/ 80	+++	
19	211	65	3 208	1 01	+++	+	+	185/110	+++	Eliminating edema
20	131	72	3 792	0 9	++	Few	+	200/140		
21	257	66	3 693	0 91	++++	+++	++	144/ 94	++	
22	270	76			+	0	Occ	210/150		Left hemiplegia
23	80	76			+	0	Occ	165/105	+	
24	8	95	4 480	1 01	++	0	+	155/107		
25	9	78	3 952	1 00	+	0	+	145/ 85		Recent edema, fibrillation
26	36	81	3 944	1 03	++++	+++	+	180/118	+++	
27	2	92	5 264	0 88	++	0	+	148/120		
28	267	80	4 472	0 9	+			135/—		Dyspnœa, cyanosis, enlarged heart
29	246	93	5 728	0 8	++++	+	+	258/138		
30	256	76	5 224	0 73	++	0	Occ	152/ 94	0	
31	80	76			+	0	Occ	165/105	+	Pleural effusion
32	259	78	5 088	0 78	Trace	0	0	98/ 66	±	
33	75	90	4 464	1 02	Trace	0	+	126/ 90		

\* Moderate degree of anemia. Items 24 to 33, inclusive, presented evidence of congestive myocardial failure.

TABLE 5—*Chronic Diffuse Nephritis (Marked Impairment of Renal Function)*\*

No	Blood Count				Urine			Blood Pressure	Edema	Comment
	Case No	Hemo globin, per Cent	Red Cells, Mil-lions	Color Index	Albu-min	Red Blood Cells	Casts			
1	296	75	4 288	0 89	++++	+	++	152/ 88	+	Recently edematous
2	28	72	3 920	0 92	++++	0	+	185/125		
3	72	72	3 008	1 2	++++	+	+	132/ 84		
4	41	35	2 440	0 72	Trace	+	+	175/100	+	Pulmonary tuberculosis
5	11	50	3 088	0 83	+++	0	+	200/140		
6	73	91	5 272	0 87	Trace	+	+	160/110		
7	79	70			+	+	+	115/ 95	+	Enlarged heart
8	293	78	5 728	0 63	Trace	0	0	186/124		
9	271	70	4 288	0 83	++++	Occ	++	268/138	+++	
10	74	90	4 081	1 1	+	0	0	180/120	+	Doubtful if nephritis, pyelitis

\* Cases 293, 271 and 74 showed congestive myocardial failure. In this and the succeeding table increasingly severe anemia occurs with the marked and maximal impairment of kidney function.



these cases showed some cyanosis or congestion. This factor was discussed under myocardial insufficiency.

With respect to case 71 (table 4), a complicating factor was a duodenal ulcer which may have had some influence in producing the anemia.

TABLE 6—*Chronic Diffuse Nephritis (Maximal Impairment of Renal Function)*

No	Blood Count				Urine			Blood Pressure	Edema	Comment
	Case No	Hemo- globin, per Cent	Red Cells, Mil lions	Color Index	Albu- min	Red Blood Cells	Casts			
1	231	55	2 816	0 98	+++++	++	+	198/128	0	Uremia Heart and liver enlarged
2	232	21	1 260	0 84	+	0	+	224/140	0	
3	238	61	3 003	1 01	+++++	0	Few	208/126		
4	240	47	2 488	0 98	+++++	Occ	+	178/110	++	Uremia Uremic signs Oliguria, uremia Uremia
5	242	50	4 160	0 6	+++++	Few	++	206/122	0	
6	261	55	2 512	1 10	+++++	0	+	178/118	+ and 0	
7	276	60	3 290	0 9	Trace			140/103		Uremia Uremic signs Uremic signs Oliguria, uremia Uremia
8	280	42	2 640	0 8	+++++	+	+	222/126		
9	285	37	2 100	0 88	+	0	+	130/ 90		
10	295	40	2 176	0 98	++++	+ and 0	++	115/ 80	++	Wassermann + Toxic uremia later retention uremia
11	300	49	2 760	0 9	+++++	+	+	192/118	+	
12	18	40	3 680	0 55	+++++	0	+	185/125		
13	20	61	3 336	0 92	+++++	0	+	160/ 90		
14	25	72	4 470	0 81	+++++	0	+	235/135		
15	27	52	3 168	0 83	++	0	+	220/150		
16	39	33	2 808	0 58	++	+	+	160/100		
17	44	65	2 300	1 41	++	0	+	210/110		
18	83		2 880		+++++	0	0	232/164	0	
19	15	60	3 176	0 96	+++++	0	+	260/160	+	
20	16	47	2 632	0 90	+++++	0	+	240/156	+	
21	17	35	1 944	0 92	+++++	0	0	202/150		
22	264	15	2 934	0 77	Trace	0	Occ	210/128		
23	278	51	3 232	0 79	+++	Few	++	215/148		
24	24	60	3 160	0 96	+++++	Rare	+	210/110		
25	14	70	3 200	1 09	+++++	++	++	153/100	++	Some cyanosis
26	26	67	2 568	1 34	+++++	0	+			
27	29	48	2 896	0 85	+++++	+++		280/150	+++	
28	67	55	3 304	0 83	++++	+ and 0	++	120/ 50	+	Aortic insufficiency
29	84	45	2 704	0 8	+++++	0	+	223/147		
30	86	60	3 290	0 93	+++	0	Occ	175/115		
31	82	87			Trace	0	Occ	180/130	0	Peritonitis Uremia
32	107	50	3 000	0 83	+++	+	+	194/118	+	
33	281	39	2 080	0 9				146/ 88	0	
34	258	78	4 480	0 88	+++++	0	Occ	205/155	+	Mitral insufficiency Liver at umbilicus Myocardial insuffi- ciency
35	45	80	3 936	1 02	++	0	+	250/170		
36	85	60	4 980	0 61	Trace			206/148	+++	
37	286	39	2 160	0 92	+++			186/120		Retention uremia, chronic passive congestion
38	284	68	4 880	0 7	+++++	+	Many	194/114		

Case 73 (table 5) exhibited a hemoglobin of 91 per cent with a red cell count of 5,272,000, though the kidney function was "severely" impaired. This was a case of pyelitis bearing a notation "doubtful if nephritis," and the functional involvement of the kidney may have been too recent or too temporary to influence the blood count.

In table 6, the one noteworthy exception to the severe anemia which most of these cases with maximal renal insufficiency show is case 82, in which the patient was a man aged 51, who died of peritonitis. The hemoglobin reading was 87 per cent. The kidneys showed cloudy

swelling at autopsy. There were cerebral arteriosclerosis, hemiplegia and "a combination form of nephritis." The kidney function had shown maximal impairment, yet the patient had apparently not died of renal insufficiency but of peritonitis. It was difficult to judge the duration of the kidney insufficiency. Presumably, if the condition of the kidney had been allowed to progress to contraction (rather than cloudy swelling), the anemia would have become manifest. Again, the cerebral arteriosclerosis and the hemiplegia indicate the possibility of the cerebral lesion having affected the blood count to induce a relatively high hemoglobin.

Effect of Infections (Granuloma).—Transfusion, a prolonged low protein diet or other forms of therapy may temporarily obscure the relationship between anemia and kidney function. The rôle of infection in accounting for part or all of the anemia must be ruled out in these cases of chronic diffuse nephritis as elsewhere. Here, however, the type of infection is apt to be different from that seen in the acute form of nephritis, being more obscure and more chronic. For example, in the nephrotic stages included in this group, tuberculosis, syphilis, pneumococcus peritonitis and other conditions must be reckoned with. The following instances may be cited from the cases tabulated under chronic diffuse nephritis: cases 131, 19, 20, syphilis, case 31, tuberculous osteomyelitis and case 41, pulmonary tuberculosis, case 5, nephrosis and healed pulmonary tuberculosis.

Myxedema, with its anemia and edema, must be distinguished from chronic nephritis or nephrosis before any comparisons are attempted between the blood count and the kidney function.

The practice of subjecting many nephritic and hypertensive patients to prolonged periods of curtailment of protein intake introduces an additional etiologic factor for the anemia that must be excluded in some cases.

Effect of Albuminuria and Edema. The effect of albuminuria and of edema is of great importance in all cases of renal insufficiency and anemia. While albuminuria may, over a long period of time, be a factor in inducing anemia in some cases, in others, with no albuminuria or edema, there is equally severe anemia. In the hypertensive group with primary contracted kidney, although albuminuria and edema are absent or only slightly in evidence as compared to the group of cases of chronic diffuse nephritis, the anemia is as severe in the former as in the latter when renal insufficiency exists.

Ewing,<sup>13</sup> in describing chronic exudative (parenchymatous) nephritis, stated that the cases with albuminuria and edema show a marked anemia, but that this is subject to great variation.

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13 Ewing, J. Clinical Pathology of the Blood, Philadelphia and New York, Lea Bros. & Company, 1903.

*Hypertension with Varying Degrees of Renal Insufficiency*—One hundred and thirty-two cases of hypertension are reviewed in tables 7 to 11 inclusive and are arranged in the order of the severity of the kidney damage. As was stated in the analysis of average results, a number of patients were found in whom congestive myocardial failure or cerebral lesions dominated the kidney symptoms. These are included in each table and classified according to the degree of renal insufficiency.

TABLE 7—*Hypertension (No Impairment of Renal Function)*

No	Blood Count				Urine			Blood Pressure	Edema	Comment
	Case No	Hemo per Cent	Red Cells, Mil-lions	Color Index	Albu-min	Red Blood Cells	Casts			
1	253	92	5 928	0.8	++++	0	0	164/120	0	
2	102	90	4 824	0.98	Trace	Few	Occ	180/135		Irregular fluid output
3	106	100			Trace	0	+	200/125	0	
4	114	90	4 912	0.9	SI tr	0	0	165/95	0	Normal except polyuria
5	121	100	5 220	0.96	Trace	0	Occ	240/120		
6	155	100			Trace	0	Occ	220/115	0	Polyuria, otherwise normal
7	157	75	4 728	0.79	++	0	Occ	250/162	0	Syphilis
8	162	91	4 664	0.98	+	0	±	210/140		
9	163	88	4 980	0.89	Trace	0	Occ	210/150		
10	171	100	5 072	1.0	v f t	0	0	230/135		
11	173	87	4 408	0.98	Trace	Few	0	200/110		Slight passive congestion
12	185	90	4 768	0.95	+	0	Occ	145/100		
13	192	85	4 608	0.92	+	0	Occ	260/160		
14	225	95			++	0	Occ	210/120	Recent	Normal except low night specific gravity
15	218	90	4 516	1.0	++++	0	+	130/75	++	Normal except slight nocturnal polyuria
16	216	95	4 416	1.07	Trace	0	Occ	220/140		Slight nocturnal polyuria
17	208	98	5 040	0.98	Ft tr	0	Occ	200/130		Oliguria, otherwise normal
18	288	84	5 024	0.84	0	0	0	208/121		Enlarged heart, preponderance l v
19	174	84	6 672	0.63	Trace	0	Occ	260/150		Congestion, enlarged liver
20	198	70	4 160	0.85	Trace	0	Rare	170/110	+	Passive congestion, myocardial insufficiency
21	197	60	5 000	0.60	+	Few	+	195/70		Heart to axillary line, enlarged liver
22	130	78	5 624	0.69	+	0	0	180/120		Myocardial insufficiency
23	160	90	5 644	0.8	0	0	0	224/155	0	Microcephalus
24	168	91	6 006	0.75	+	0	Occ	220/135		Cerebral arterio sclerosis, cyanosis, slurs words

\* The uncomplicated cases show essentially normal blood counts. Items 18 to 22 are "cardiac" and items 23 and 24 are "brain" cases.

In the hypertensive group as elsewhere, the anemia parallels the extent of involvement of kidney function in the vast majority of cases. Among the seventeen cases with no impairment (table 7), the hemoglobin was 90 per cent or over and the red cells 4,400,000 and more in thirteen cases. When the cases with slight renal insufficiency are examined (table 8), the hemoglobin and red cells are also found to be high in the majority. An increasingly larger number of cases with hemoglobin of

70 plus per cent begin to appear when moderate renal insufficiency has ensued (table 9), and in the cases with marked and maximal insufficiency (tables 10 and 11) hemoglobin values of 65 per cent, 55 per cent and 45 per cent, with red cell counts of from 2,500,000 to 3,250,000 dominate the picture

TABLE 8—*Hypertension (Slight Impairment of Renal Function)* \*

No	Blood Count				Urine			Blood Pressure	Edema	Comment
	Case No	Hemo- globin, Cent	Red Cells, Mil- lions	Color Index	Albu- min	Red Blood Cells	Casts			
1	139	92	5 752	0 8	0	0	Rare	168/112	0	
2	101	96	4 484	1 09	Trace	0	Ooc	220/175		Pleural effusion
3	115	85	1 984	0 86	+	0	Rare	175/ 90		Slight hyposthenuria
4	120	85	4 800	0 88	+	Catheter	Rare	180/100		
5	124	91	4 520	1 01	±	0	Rare	155/100	0	Syphilis aortic insufficiency
6	125	82	5 260	0 78	++++	Few	+	245/135	0	Syphilis
7	127	92	5 234	0 88	+	0	+	238/120	+	Enlarged liver, myo- cardial insufficiency
8	128	80	4 640	0 86	0	0	0	200/100		
9	129	70	4 688	0 76	Trace	0	Ooc	168/105		Amyotrophic lat- eral sclerosis
10	146	93	5 164	0 91	++++	0	+	220/175	+	Nonprotein nitro- gen 2S
11	154	80			Ft tr	0	+	192/124	0	
12	158	80	4 768	0 85	0	0	0	144/ 92	0	
13	177	75	5 310	0 70	+	0	+	250/160		Cardiac hyper- trophy
14	186	83	4 608	0 90	Ft tr	0	+	180/110	0	Oliguria
15	194	88	4 312	1 02	++++	0	+	210/160		Oliguria
16	196	77	4 584	0 85	Trace	0	+	240/160	0	
17	205	93	5 320	0 87	Ft tr	0	+	190/140	0	Kidney fatigue, non- protein nitrogen 2S
18	214	85	4 352	0 98	Ft tr	0	+	220/120		
19	228	80	4 192	0 97				200/140		
20	178	80	4 912	0 81	+++ & trace	0	+	255/160		Heart 4 × 17 cm, 6th interspace
21	180	78	3 600	1 08	0	0	Rare	180/105	+	Myocarditis, oliguria
22	182	85	5 152	0 83	0	0	0	160/—		Heart enlarged to right and left
23	210	85	1 352	0 98	0	0	0	165/ 95	0	Dilated aorta
24	213	65	3 296	1 01	+ and 0	0	0	170/ 95		Myocardial insuffi- ciency
25	199	95	5 280	0 91	Trace	0	+	170/100		Enlarged heart, oliguria
26	214	67	4 672	0 7	++++	Rare	+	166/ 88	+	Heart 17 cm to left, 6th interspace
27	182	95	4 584	1 05	Trace	0	+	210/110	0	Pseudobulbar palsy
28	159	103	4 920	1 05				185/125	0	Explosive headaches
29	167	93	4 762	0 98	Trace	0	Ooc	220/150		Cerebral arterio- sclerosis
30	175	82	4 060	1 02	Trace	0	0	200/145		General arterio- sclerosis
31	176	80	4 224	0 95	+	0	+	197/130		Left hemiplegia, extrasystole

\* The uncomplicated cases show no or slight anemia. Items 20 to 26 showed myocardial failure. Items 27 to 31 showed "cerebral" symptoms.

From a study of seventy-six patients with hypertension and arterio-sclerosis, Adams and Brown<sup>12</sup> concluded that anemia was related to the renal insufficiency. Among the seventy-nine cases itemized in tables 7 to 11 inclusive, some do not show the close parallel between renal function and anemia which obtains for most cases, even when not complicated by myocardial insufficiency or cerebral insult. These do not

necessarily disprove the general rule, in fact, they confirm the views with regard to the effect of myocardial changes, infection, etc., which have been presented previously. Brief additional data are here submitted which may aid in the interpretation of these cases.

TABLE 9—*Hypertension (Moderate Impairment of Renal Function) \**

No	Blood Count				Urine			Blood Pressure	Edema	Comment
	Case No	Hemo- globin, Cent	Red Cells, Mil- lions	Color Index	Albu- min	Red Blood Cells	Casts			
1	94	90	5 540	0 81	Trace	0	+	180/105		
2	150	80	4 200	0 95	Ft tr	0	0	195/115	±	Cardiac edema ?
3	151	83			++++	+++	+	230/162		Urethritis
4	152	64			Ft and 0	0	Occ	250/140		
5	140	80	5 088	0 80	Ft tr	0	+	205/140	0	
6	141	89	4 360	1 03	Tr to	0	++	160/120		Myocardial degener- ation, oliguria
7	142	75			0	0	0	185/105	0	
8	133	68	4 304	0 81	+ and 0	+	0	220/145		
9	134	100	4 960	1 02	++	0	+	124/ 85	±	Transient hyper- tension
10	166	70			+	0	Occ	270/170	0	Arrhythmia
11	172	87	4 464	0 98	v i t	0	Rare	240/120	±	Cardiac edema ?
12	201	75	5 000	0 75	Trace	0	Occ	170/ 90	±	Incipient contracted kidney
13	204	70	5 512	0 63	++	0	0	230/168		Nonprotein nitro- gen 33
14	227	86	4 904	0 87	++	0	0	240/135	±	Right heart slightly enlarged
15	13	74	4 300	0 9	++	Menses		260/—	0	Peritonitis, hemor- rhage
16	290	79	4 530	0 87	Trace	0	0	218/148	0	Headache blurred vision
17	98	72	4 792	0 76	Trace	0	+	170/100	0	Slight cyanosis
18	153	90			Trace	0	+	210/115	+	Nonprotein nitro- gen 29
19	148	96	5 520	0 87	Trace	0	+	175/100		
20	117	100	5 936	0 84	Trace	0	+	240/155	Cardiac	Pontile hemorrhage decompensation
21	143	72	5 920	0 61	Trace	0	Rare	155/100	++	General edema, chronic passive congestion
22	133	83	4 720	0 88	+	Few	+	215/115	0	Aortic insufficiency
23	137	65	4 300	0 75	++	0	0	170/ 90	0	Recent myocardial insufficiency
24	138	84	5 064	0 84	+	0	+	170/120	0	Myocardial insuffi- ciency, enlarged liver
25	135	103	6 304	0 81	Trace	Rare	+	180/105		Syphilis, pleural effusion
26	170	90	4 576	1 0	Ft tr	0	Occ	212/135		Mitral endocarditis
27	209	84	4 600	0 91	Trace	0	0	165/110		Congestion
28	212	74	4 856	0 77	±	0	0	300/175		Passive congestion
29	118	67	4 920	0 68	++	0	+	190/115		Polyuria, compen- sating myocardial insufficiency
30	181	68	3 834	0 89	+	0	+	220/135		Pleural effusion enlarged liver
31	149	84	5 184	0 82	0	0	0	"Normal"		Emphysema
32	224	88	5 132	0 86	+	0	0	240/140		Erythremia, mitral insufficiency
33	161	110	5 368	1 03	+	0	+	245/140	+	Polycythemia, marked headache
34	169	100	4 128	1 2	0	0	0	240/160		Right hemiplegia
35	217	95	5 376	0 89	Trace	0	0	230/125		Polycythemia, con- vulsions
36	223	98	5 400	0 90	Trace	0	+	200/135	0	Convulsions, uremia (?)

\* Moderate anemia in many cases. Items 17 to 32 presented congestive myocardial failure and items 33 to 36 manifestations of "brain" disease.

The patient in case 157 (table 7), a woman, aged 34, showed a hemoglobin of 75 per cent though the kidney function was normal. This patient was syphilitic, with evidence of an enlarged heart, and the whole blood count with its "anemia of haemoglobin only," gave indication of a cardiac picture. This case was not classified with the cardiac cases because no notes were available as to whether or not there was insufficiency. Here too, the anemia may have been a result of a recent exaggerated stage of chronic diffuse nephritis, of which she gave a history.

TABLE 10—*Hypertension (Marked Impairment of Renal Function)* \*

No	Case No	Blood Count			Urine			Blood Pressure	Edema	Comment
		Hemo- globin, per Cent	Red Cells, Mil- lions	Color Index	Albu- min	Red Blood Cells	Casts			
1	239	52	3 190	0 83	+++	0	+	240/150		Macrocytes
2	274	45			+++	0	+	250/130		
3	283	65	3 608	0 9	+++	Few	+	209/130	+	
4	298	67	3 912	0 85	++			200/150		
5	93	65	3 984	0 83	Trace	0	Occ	210/ 85		
6	188	72	4 600	0 78	+	0	Occ	220/148		
7	200	85	4 496	0 96	+++	0	+	248/154		
8	215	70	3 408	1 02	Trace	0	+	200/150		Tuberculosis of right apex
9	279	55	3 981	0 70	+++	0	+	235/140	++++	Pleural and perito- neal effusion syph- ilitic aortic sclerosis Uremia
10	226	75	4 640	0 81	+ and 0	0	+	245/165		
11	156	86	4 368	1 0	Trace	++	0	195/105		
12	266	80	5 288	0 76	++	0	Occ	215/120	++	Myocardial insuffi- ciency, enlarged liver
13	91	66	3 912	0 84	++++	0	+	240/140		Heart, 6th space, mitral insufficiency
14	109	72	4 064	0 9	+	Occ	+	240/140	+	Heart, 6th space
15	202	60	2 876	1 07	0	Few	0	175/ 95	+	Wassermann +, pleural effusion
16	74	90	4 081	1 1	+	0	0	180/120		Left hydrothorax, myocarditis, insufficiency
17	183	80	6 688	0 6	+	0	0			Aneurysm, thoracic aorta
18	184	92	7 332	0 63	0	0	0	220/140		Polycythemia, cerebral arterio- sclerosis

\* In this and the succeeding table, the anemia becomes marked "Heart" and "Brain" cases are indicated

In case 129 (table 8), that of a man, aged 59, the anemia is out of proportion to the slight degree of kidney dysfunction. This patient suffered from amyotrophic lateral sclerosis.

In case 94 (table 9), the patient, a man, aged 47, exhibited no anemia with moderate impairment of renal function. No significant data other than those given in the table are available. One may speculate as to whether or not the duration of the moderate insufficiency, at the time of the blood count recorded, was too short to produce an anemia. Reference may be made to the note regarding case 134.

In case 141 (table 9), the relatively higher hemoglobin and red cell count than might be expected with moderate renal insufficiency may be related to the myocardial degeneration and oliguria

In case 134 (table 9), the patient, a man, aged 23, was the subject of moderately impaired renal function, yet his hemoglobin and red cells were 100 per cent and 4,960,000, respectively. This patient's record bears a comment which serves to explain the discrepancy not only in his case but possibly in that in case 94 (table 9). The note is made that the "elevated blood pressure was transient." Presumably, it was not of sufficient duration to affect the blood count. In fact, the blood pressure recorded in conjunction with the blood count was normal, 124 systolic and 85 diastolic, though it had previously been elevated.

Cases 172 and 227 in table 9 showed clinical signs which might put them on the borderline with regard to their classification as cardiac cases, in these, congestion, which they exhibited, may account for a somewhat higher blood count than the degree of kidney insufficiency warrants. In addition, it must be pointed out that case 227, while classified under moderately impaired function, bears the comment that the renal function varied from normal to moderately impaired, so that a hemoglobin content of 86 per cent and 4,904,000 red cells are consistent.

Lest undue discussion of these few exceptions detract attention from the main tendency, the conclusion is again stated that in nearly all of the uncomplicated cases of hypertension, as in acute or chronic diffuse nephritis, the renal insufficiency is matched by an anemia which closely reflects the degree of involvement of kidney function.

*Myocardial Insufficiency*—In the tables citing the cases of diffuse nephritis and of hypertension are found data for patients in whom the hemoglobin percentage and more particularly the red blood cell counts are higher than are the corresponding figures in the same stage of renal dysfunction for the majority of the patients. In most of these cases, the hemoglobin more nearly parallels the kidney function, whereas the red cells are normal or relatively high. These are instances of myocardial insufficiency.

The disparity between hemoglobin and red cells enables one to describe these cases as having an "anemia of haemoglobin only" and characterizes them by a low color index. So far as these facts apply to cardiac disease, they are well known. The present study, by including kidney function, presents the older knowledge in such a light as to permit its use in differential diagnosis and in the recognition of a myocardial complication during the course of nephritis or hypertension.

It is an interesting, although in a measure disturbing, commentary that references to the blood count in nephritis and in myocardial decompensation are to be found in works on hematology and are extremely meager or entirely lacking in the works on nephritis or on heart disease. Writing on the subject of acquired heart disease, Gulland and Goodall<sup>10</sup> have said, "Some high red counts have been recorded. The number of red corpuscles is not usually raised in fully compensated valvular

TABLE 11—*Hypertension (Maximal Impairment of Renal Function)*

No	Blood Count				Urine			Blood Pressure	Edema	Comment
	Case No	Hemo- globin, per Cent	Red Cells, Mil- lions	Color Index	Albu- min	Red Blood Cells	Casts			
1	69	55	3 160	0 88	++++	0	+	247/185	±	
2	92	75	4 776	0 79	+++	Menses	0	260/154	+	
3	104	86	4 272	1 02	++++		++	223/150		
4	108	65	3 744	0 87	Trace	0	+	200/105		
5	110	46	2 592	0 92	++	0	0	206/140		
6	165	60	3 937	0 76	Trace	0	Occ	210/145		
7	187	64	3 248	1 0	++	0	+	220/135		
8	189	70	3 908	0 89	++++	0	++	270/200	+	
9	190	58	4 360	0 67	++	0	±	240/180	+	Pleural effusion recent myocardial insufficiency
10	191	45	2 528	0 90	++++	0	++	240/150	+	
11	195	45	3 068	0 75	+	0	0	230/157	+	
12	206	46	2 824	0 82	++++	0	++	230/140		Uremia
13	265	72	3 368	1 09	Trace	0	0	182/100	+	Uremia, emphysema, cyanosis
14	64	52	3 408	0 76	++++	+	+++	280/150	+++	Hypertrophic and dilated heart
15	193	78	3 808	1 02	+	0	+	110/85		Heart dilated to right
16	99	55	2 976	0 94	+	0	+		++	Pleural effusion, myocardial insufficiency
17	112	103	5 512	0 93	+	0	+	255/185	0	Enlarged heart
18	113	72	5 400	0 66	+++ to ++	0	++	205/140	Recent	Recent pleural effusion
19	144	78	5 112	0 76	++	0	++	140/110	Recent	
20	164	65	4 440	0 73	++++	0	++	200/130	0	Slight myocardial insufficiency
21	145	70	5 088	0 7	++++	0	++	205/105	Slight	Recovering from myocardial insufficiency
22	268	47	2 670	0 9	++++	+	++	210/130	+	Enlarged heart
23	207	100			++++	0	+	230/110	+++	Myocardial insufficiency, angina pectoris, pleural effusion

disease but it is usually above the normal in mitral disease when compensation has failed, and in many conditions of dilatation and chronic strain (emphysema, chronic bronchitis) without valvular disease, in which the compensation is inadequate."

It is worthy of comment that the authors refer to "high red counts" and to "the number of red corpuscles" rather than to the hemoglobin, which is precisely the picture that the tables show. Instances of the "chronic strain without valvular disease in which compensation is inadequate" are cases 259 (table 4) with emphysema and bronchiectasis and 149 (table 9), with emphysema.



Ewing<sup>13</sup> reported with reference to the blood count in chronic endocarditis "When chronic venous stasis is established and dyspnea, cyanosis and edema exist, the changes are more complicated. Under these circumstances the blood loses water, becomes richer in red cells, and more so in the capillaries than in the veins. The constant tendency toward anemia is usually masked by the peculiar condition of the circulation."

*Cerebral Lesions*—In any study of hypertensive patients a certain proportion will be found in whom the blood vessels of the brain have borne the brunt of the increased blood pressure. Twelve such cases are among the 132 now reported. When the characteristic high normal or polycythemic blood counts of most of these cases were noted, five patients with known polycythemia were examined as controls in order to see whether these too showed evidence of cerebral lesions. This positive relationship has been discussed in the earlier part of this paper.

Cerebral arteriosclerosis, headache, slurring speech, pseudobulbar palsy, hemiplegia, convulsions, parkinsonian tremor and focal occlusion of blood vessels are among the clinical and postmortem diagnoses in this group. Ten of the twelve original patients had hemoglobin readings of 90 per cent or over, in contrast to the low hemoglobin of myocardial insufficiency. In six cases the red cells were 5,000,000 or over, whether the renal function was normal or impaired. Case 168 (table 7) may be cited as an example. The patient, a man, aged 56, gave evidence of cerebral arteriosclerosis, his speech was slurred, he was cyanotic. His blood count showed 91 per cent hemoglobin and 6,006,000 red blood cells.

The preponderance of symptoms and signs referable to the nervous system must not cause one to lose sight of the kidney and cardiac changes which a small proportion of these cases show. Thus in case 183 (table 10) vascular nephritis with marked degree of impairment of function, and thoracic aneurysm seemed, at least at the time the blood counts were made, to be the chief lesions. In a control case (248) with 110 hemoglobin and 8,152,000 red cells the patient was troubled with angina pectoris. Lamson<sup>8</sup> described the polycythemia which may occur in cases of chronic cardiac disease with interference of the pulmonary circulation. Here the blood count represents an effect which is, in a sense, an exaggeration of the high red counts described under myocardial insufficiency. Whether or not these patients subsequently suffered a cerebral insult or were carried off by a cardiac or kidney disease or by an "intercurrent" pathologic condition before such an event, is of course problematic. The burden of evidence from the literature and from the pathologic changes cited in the cases included in the present study predicts cerebral damage for most of these patients.

While most of these patients present an "apoplectic" appearance with slight congestion or cyanosis, this symptom may be lacking even though the blood count is unusually elevated. Hess, quoted by Lamson,<sup>8</sup> and Gulland and Goodall<sup>10</sup> have remarked that cyanosis may be absent. In some instances an unusually high blood count is found, although there is extreme pallor. An illustration of this phenomenon is a control case (100), that of a man, aged 26, with marked hypertension (220 systolic and 130 diastolic), generalized arteriosclerosis and excruciating headache. The urea nitrogen of the blood was normal and the urine had a specific gravity of 1020 with a trace of albumin. Despite an extreme, lemon-yellow pallor, a blood count showed 106 hemoglobin and 6,500,000 red cells.

The viscosity of the blood of the patients in this group may be high, and speculation has arisen as to what extent this is an influence in the causation of the cerebral lesions. The patient in case 248 with polycythemia and angina pectoris had a viscosity reading of 10.8.

#### COLOR INDEX (NATURE OF THE ANEMIA)

The normal color index must be taken as about 1 (Thro,<sup>14</sup> 15). Meyer and Butterfield,<sup>15</sup> in Friedrich Muller's clinic at Munich, found normal cases in which the index was 1.1 when the Sahli method for hemoglobin determination was employed.

*Renal Insufficiency*—In the case of renal insufficiency the average color index values were approximately 0.9. This does not reflect the clinical picture, since marked variations occur. At times the anemia is of an extreme secondary type, and at others it resembles the pernicious type with the color index close to and greater than 1. The latter state is more frequently seen in patients with marked and maximal renal insufficiency, in whom one is apt to find a yellow pallor.

Ewing,<sup>13</sup> in 1903, attributed the "relatively high hemoglobin index" occurring in chronic exudative (parenchymatous) nephritis to the "loss of albumin which affects principally the serum." He continued, "Grave or pernicious anemia develops in a small proportion of cases of chronic parenchymatous nephritis and appears at times to result directly from the nephritis. It must be referred to the repeated losses of albumin from the blood and to the general disturbance of nutrition, but it is probable that the very severe grades of anemia result from the combined effects of lesions in several viscera, including gastritis, cirrhosis of the liver, arteriosclerosis, etc."

14 Thro, W. Clinical Laboratory Methods, New York, J. T. Willson, 1920.

15 Meyer, E., and Butterfield, E. E. The Color Index of the Red Blood Corpuscles, Arch. Int. Med. **14** 94 (July) 1914.

Berg,<sup>16</sup> in 1922, reported a series of cases of nephritis showing that the patients with retention of nitrogen were apt to have a color index of from 0.9 to 1.1

Mayers,<sup>17</sup> reporting on cases of uremia, recorded blood counts in which, though the color index is not stated, calculation gives figures of 1 plus as the indexes

The relationship of these observations to liver injury is suggested by Ewing's statement already mentioned and by the fact that similar indexes as well as pathologic changes in the liver are encountered in primary pernicious anemia. Ewing<sup>18</sup> emphasized the fact that in chronic Bright's disease changes in the liver are frequent. Capillary congestion and distention and areas of edema are among the lesions of the liver that he mentioned. In experimental uremia, Andrews<sup>19</sup> observed degeneration of the cytoplasm of the liver cells. In a case of chronic nephritis with a marked "nephrotic element," recently observed in a child, the same type of fatty infiltration was found in the liver cells as in the tubules and interstitial tissues of the kidneys. It has been observed that the kidneys of cattle yielded beneficial therapeutic results when fed to patients with pernicious anemia. In experimental uremia and in "ether nephritides" of dogs, Andrews and Thomas<sup>20</sup> found that the first blood-free proteins passed in the urine had their origin in the liver. These facts further suggested a relationship between the liver and kidney. At the present stage of knowledge, definite conclusions on this issue cannot be drawn. The point may be made, however, that a high color index may be a clue to a diagnosis of renal insufficiency apart from the nephritis which sometimes complicates primary pernicious anemia. Excluding the case of pernicious anemia introduced as a control, forty-three of the 299 cases in this study manifested a color index over 1. In nineteen of these the hemoglobin and red cell count were normal, so that these may be considered as coming under Meyer and Butterfield's<sup>15</sup> description of the high normal value for the color index. The remaining twenty-four cases of high index occurred when the red cells and hemoglobin were reduced, so that these truly reflect the incidence of this type of anemia. They were observed with chronic diffuse nephritis or with primary contracted kidney.

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16 Berg, N. N. Observations on the Blood in Cases of Chronic Nephritis Associated with Nitrogen Retention, *Am J M Sc* **164** 88 (July) 1922

17 Mayers, L. H. Clinical Variations of Uremia, *J A M A* **88** 97 (Jan 8) 1927

18 Ewing, J. Lectures on Pathology to Cornell Medical School Students, Lecture Notes taken by present writer

19 Andrews, E. Experimental Uremia, *Arch Int Med* **40** 548 (Oct) 1927

20 Andrews, E., and Thomas, W. A. The Origin of Urinary Proteins, *J A M A* **90** 539 (Feb 18) 1928

Brown and Roth<sup>21</sup> concluded that hemolysis was not the etiologic factor in the anemia of chronic glomerular nephritis and ascribed the anemia to decreased function of the bone-marrow. If decreased blood formation is the cause, these color indexes must be interpreted as indicating an "aplastic type" of pernicious anemia, though on the other hand, it is known that after a time, hemolytic types of anemia may merge into aplastic types.

Macrocytes are rarely found,<sup>16</sup> they were noted in only one patient of this series, case 239 (table 10). Microcytes are usually reported.

*Myocardial Insufficiency*—In the cases of myocardial insufficiency, as might be expected from the large number of relatively pale cells that congest the peripheral circulation, the denominator of the fraction of hemoglobin over red cells being increased, a low color index is usually observed. While not applicable to all cases on account of the extreme variation, it may be suggested that a high color index points toward renal insufficiency, while a low index indicates congestive myocardial failure.

*Cerebral Lesions*—In the cases manifesting cerebral lesions, the average color index is about 0.9, though low indexes may be encountered because usually in polycythemia the red cells are proportionately more increased than is the hemoglobin (Lamson<sup>8</sup>). The low index here is differentiated from that in myocardial failure by the low hemoglobin of cardiac insufficiency as compared to the high value in polycythemia.

#### THE EFFECT OF ANEMIA ON KIDNEY FUNCTION

The question may well be raised as to whether or not the anemia itself does not aggravate or cause the nephritis with which it is associated. As is well known, pernicious anemia is often complicated by chronic productive nephritis. Many years ago, it was observed that secondary anemia produced changes in the kidney. The situation, so far as it bears on the present paper, may be summarized by saying that while the anemia undoubtedly imposes additional burdens on the heart and kidneys of these patients, thus forming a "vicious circle," the history and clinical course of the cases in this study clearly point to the fact of a nephritis antedating the anemia. Furthermore, in a study of four control cases in which the primary disease was anemia (one of which is that of a true pernicious anemia), it was evident that the blood dyscrasia was much more marked than was the degree of impairment of kidney function. This is the converse of what usually obtains in cases of nephritis. In a case of cancer of the bladder, the anemia was characterized by a hemoglobin as low as 37 per cent and a red cell count of only 2,448,000, yet the kidney function was only slightly to moderately impaired. In a case (250) of primary pernicious anemia the disease was known to have existed for over two years, yet the kidney function was normal, though the hemoglobin was 70 per cent and the erythrocytes numbered 2,880,000.

21 Brown and Roth (footnote 3, first reference)

## CONCLUSIONS

The blood count is of value in estimating the relative importance of the kidney, the heart and the cerebral blood vessels in inducing the combination of signs and symptoms which make up the different stages and types of "cardiovascular renal" disease

1 A secondary anemia is invariably associated with and is directly proportional to the degree of impairment of renal function

(a) This relationship holds true for renal insufficiency from any cause. It applies whether the nephritis is acute or chronic, glomerular or diffuse, primary or secondary contraction, or whether the diminution of kidney function is due to conditions other than Bright's disease, as, for example, polycystic kidney or nephrectomy

(b) Hematuria, infection, albuminuria, edema, myxedema, restricted protein intake, etc., produce an anemia which occurs independently of the lowered red cell count that accompanies impaired renal function, all these influences must be considered in interpreting the significance of the blood picture

(c) In a small proportion of the cases with marked and maximal renal insufficiency, the anemia is characterized by a color index greater than 1. The possible relation of this feature to pathologic changes in the liver is discussed

2 The blood count may furnish a clue as to the coexistence of congestive myocardial failure or cerebral lesions

(a) The cardiac cases exhibit a low hemoglobin percentage which in a measure parallels the renal insufficiency, while the red cell count is normal or relatively high even when the kidney impairment is extreme, the color index in cases of myocardial failure is, therefore, distinctly low

(b) The "cerebral" cases are characterized by a high normal or polycythemic blood count (of hemoglobin as well as of red blood cells) whether the kidney function is normal or markedly damaged. This serves to distinguish these hypertensive cases from those in which the kidney lesion or the myocardial insufficiency is the dominating factor

# THE EFFECT OF SODIUM CHLORIDE ON HYPERTENSION \*

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In 1904, Ambard and Beaujard,<sup>1</sup> in France, put forth the claim that there was a direct relationship between the retention of sodium chloride and the level of arterial tension. This was followed by attempts on the part of French clinicians to treat patients with an elevated blood pressure by reducing the sodium chloride intake. In this country, Allen and his pupils have been the chief advocates of this method of treating hypertensive patients, while Mosenthal and his co-workers have led the opposition to this form of therapy.

In 1922, Allen and Sherrill<sup>2</sup> reported on 180 cases of hypertension in which the patients were treated by close restriction of the sodium chloride intake. Fully normal blood pressure was restored in 18.9 per cent of these patients, while in 41.9 per cent there was sufficient improvement to regard the outcome as "a distinct therapeutic success." Transitory benefit followed by relapse or death resulted in 8.9 per cent of the patients, while complete failure occurred in 30.5 per cent of the cases. The failures were believed to be due to organic changes, chiefly in the kidneys. In this report Allen set up plasma chlorides of 580 mg as a dividing line, and stated that patients with plasma chlorides above this figure had a much better prognosis than those with chlorides below this level.

Isolated case reports favorable to this line of therapy were also published by Musser,<sup>3</sup> by Konikow and Smith,<sup>4</sup> by Houghton<sup>5</sup> and by others at about the same time.

In 1923, Selman<sup>6</sup> (one of Allen's co-workers) reported ten more cases of hypertension in which the patients were treated by salt restric-

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1 Ambard, L., and Beaujard. *Arch. gen. de med.* **81**: 520, 1904.

2 Allen, F. M., and Sherrill, J. W. *J. Metab. Research* **2**: 429, 1922.

3 Musser, J. H. *New York M. J.* **112**: 570, 1920.

4 Konikow, M. J., and Smith, M. *Boston M. & S. J.* **185**: 281, 1921.

5 Houghton, H. A. *M. Rec.* **101**: 441, 1922.

6 Selman, J. J. *Ohio State M. J.* **19**: 852, 1923.

tion with reduction to normal pressure in 60 per cent of the cases. In 1925, Allen<sup>7</sup> again reiterated his statements previously made and claimed striking success in 60 per cent of his cases. He said that he also believed the salt restriction to be of benefit in mitigating the symptoms and prolonging life even in the majority of cases classed as failures. Furthermore, he stated that others who had obtained no benefits from salt-free diets in hypertension had failed because their diets were not accurately salt free.

Carrying on Allen's work, Vogel<sup>8</sup> recently reported the results in 212 cases of hypertension in which the patients had been treated at Allen's institute since the report of 1922. Seventy-four per cent of these patients were improved, while 26 per cent were classed as unimproved. In the majority of the unimproved cases, the patients were thought to have had an associated nephritis.

In opposition to the claims of Allen and his co-workers, O'Hare,<sup>9</sup> in 1921, arranged a series of forty-five cases of hypertension according to the height of the maximum blood chlorides and showed that those with the normal chloride values averaged the higher blood pressures. In 1922, Mosenthal<sup>10</sup> showed that there was no close relationship between the blood pressure and the concentration of salt in the blood, and furthermore, that types of nephritis characterized by salt retention have as their outstanding features albuminuria, edema and no increase in blood pressure. Moreover, he had not succeeded in affecting the arterial tension by the administration of 10 Gm of sodium chloride per day. In 1923, Mosenthal and Short<sup>11</sup> once more reiterated their claims of the inefficacy of sodium chloride restriction as a therapeutic measure in cases of hypertension. They emphasized the marked spontaneous variations which occur in the blood pressure of all hypertensive persons and showed that there was no evidence that sodium chloride raises the blood pressure. They concluded that sodium chloride may be safely administered in large doses to patients with hypertension, provided that there are no complications or sequelae present.

As an interesting sidelight on this question, mention may here be made of the work of Addison,<sup>12</sup> who claimed that it was the sodium and not the chloride ion which was harmful to patients with hypertension, and he treated these patients with potassium chloride.

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7 Allen, F. M. *New York State J. Med.* **25** 726, 1925.

8 Vogel, S. A. *New York State J. Med.* **28** 318, 1928.

9 O'Hare, I. P. *Proc. Am. Soc. for Clin. Invest.*, 1921, p. 6.

10 Mosenthal, H. O. *M. Clin. N. Amer.* **5** 1139, 1922.

11 Mosenthal, H. O., and Short, J. J. *Am. J. M. Sc.* **165** 531, 1923.

12 Addison, W. L. T., and Clark, H. G. *Canad. M. A. J.* **15** 913, 1925.  
Addison, W. L. T. *Canad. M. A. J.* **18** 281, 1928.

## METHOD

The purpose in this work was to determine the effects of various amounts of sodium chloride in the dietary of patients with hypertension. This has been attempted in a series of thoroughly controlled and carefully studied cases. We have also checked the results in two of these cases by repeating the sodium chloride studies after waiting several months. The difficulties encountered in such a study are numerous. In the first place, we have found it necessary to hospitalize our patients, as otherwise no accurate check could be kept on the diets. In the second place, daily determinations of sodium chloride had to be run on the specimens of urine to act as controls on the daily salt intake. Moreover, we have found that symptoms of salt privation prevented prolonged administration of diets containing less than 1 Gm. of sodium chloride per day. Also we must not omit the fact that patients usually find diets with a low salt content rather unpalatable and object to keeping up this regimen for a long period, after a while they tend to begin to "cheat" on the diet.

We have purposely refrained from using the term "salt-free" in connection with diets, as there is, accurately speaking, no such a thing as a strictly salt-free diet. Instead, we have designated our diets as salt-poor when they contained less than 2 Gm. of sodium chloride per day and as very poor in salt when they contained less than 1 Gm. of sodium chloride per day. In order to go to the opposite extreme in our tests we have also given these patients 10, 20 and even 30 Gm. of sodium chloride per day in addition to the amount present in the diet, and in some cases have also tried the effect of large doses of sodium chloride intravenously. It must be emphasized also that all our diets have been checked by daily determinations of the chloride in the urine.

In these patients we endeavored to vary the daily salt intake while keeping all the other factors as constant as possible. We also first observed the patients on an unrestricted diet for a period of time until they had become accustomed to hospital routine and their pressures had reached as stable a level as is possible with this type of patient (whose blood pressure, as we all know, is subject to frequent spontaneous variations).

We here report the results of varying the sodium chloride intake of eleven patients with hypertension. In addition, we made two distinct studies on two of these patients at different times. The average stay in the hospital was thirty-nine days, the shortest stay was nineteen and the longest seventy-five days. These patients ranged in ages from 31 to 57 years. Three were men and eight were women. Nine were white and two were colored. All of these cases belong to those commonly classified under the heading "essential hypertension", that is, the patients had elevated blood pressure without evidence of real kidney



damage and without any other readily ascertainable cause for the increased tension. The heart rate was regular in all cases. The pressures at the time of admissions varied from 150 systolic and 100 diastolic to 264 systolic and 134 diastolic. Diabetes (of a mild type) was present in one case, otherwise there were no complications.

In addition to these patients, we have also made observations on the effect of changes in the sodium chloride intake on the blood pressure of two other patients—one with nephrosis (for fifty-three days) and the other with acute glomerular nephritis (for eighty-one days).

With all the other factors constant as far as possible, the patients were kept on salt-poor diets and on diets containing varying amounts of salt for a sufficient length of time to observe whether there was any relationship between the pressure and the diet.

TABLE 1—*Summary of Blood Pressures on Varying Salt Intakes*

Case			Unrestricted Diet	Low Salt (Less Than 2 Gm/Day)	Very Low Salt (Less Than 1 Gm/Day)	5 Gm Salt/Day	10 Gm Salt/Day	15 Gm Salt/Day	20 Gm Salt/Day	25 Gm Salt/Day	30 Gm Salt/Day
1	A	S	184/110	198/123			201/119	214/127			
2	J	F	223/109		230/104		242/112	236/112		237/117	
3	F	R	201/110	194/111	195/112						
3	F	R	219/117	216/117			215/111	225/113			
4	W	G	195/124		190/118						
5	N	W	220/125	217/132			201/121	204/122	203/119		
6	L	K	174/96		168/98		142/95				
6	L	K	164/90	183/110	189/110						
7	C	W	152/94	138/98	155/95						
8	G	S	200/112		185/109						
9	S	B	166/92		152/102		148/99				
10	D	L	186/102		156/99		182/118				
11	E	K	221/100		206/95		194/91				
12	L	R	136/72	109/77			115/77	109/71			119/82
		(Nephrosis)		121/83							
13	J	R (age 11)	164/92			133/76					
		Acute Nephritis									

In order to conserve space, we reproduce only four of the charts, showing the daily (or twice daily) blood pressure readings, the daily chloride output and the salt intake. In reporting our cases, we think it would be too confusing for the reader and would take up too much of his time to give all the pressure readings, and we are therefore giving only the average blood pressure level on each type of diet in each case. Table 1 gives a summary of the average blood pressure levels in each patient under the varying amounts of salt intake.

Before going on to the case reports, it is worth while to emphasize that patients with hypertension commonly show spontaneous variation from day to day and even during the course of the same day. Deductions from the pressure curves must therefore be made with great caution, and only appreciable changes in pressure which are maintained over a period of time should be considered as having any significance. In order that the personal equation might be eliminated as far as pos-

sible, variations in the salt intake were made without the knowledge of those recording the blood pressure

#### REPORT OF CASES

CASE 1—A S, a woman, aged 52, was admitted to the hospital on June 20, 1923, and was discharged on Aug 10, 1923. Her chief complaints were precordial pain, backache and generalized weakness, also dizziness, shortness of breath and palpitation. The symptoms dated back about five years and had been growing progressively worse. The blood pressure at the time of admission was 200 systolic and 120 diastolic. The results of further physical examination were essentially negative. The orthodiagram showed widening of the ascending and descending aorta and moderate enlargement of the heart to the left. The urine showed small amounts of albumin, hyaline and granular casts and white blood cells. The blood chemistry was normal. The plasma chlorides were 597 mg per hundred cubic centimeters.

With the patient on a routine house diet, the blood pressure averaged 184 systolic and 110 diastolic, on a salt-poor diet, 198 systolic and 123 diastolic, on 10 Gm of salt per day, 210 systolic and 119 diastolic and on 15 Gm of salt per day 214 systolic and 127 diastolic.

CASE 2—J F, a man, aged 55, was admitted to the hospital on July 19, 1923, and was discharged on Aug 30, 1923. His symptoms dated back about six and one-half years and consisted chiefly of ringing in the ears, dizziness, pain in the legs and shortness of breath on exertion. The blood pressure was 230 systolic and 110 diastolic. There were no signs of decompensation. The orthodiagram showed considerable enlargement of the heart to the left and also some widening of the aorta. The urine showed a faint trace of albumin and a few casts and white blood cells. The blood chemistry was normal, and the plasma chlorides were 578 mg per hundred cubic centimeters.

The average blood pressure with the patient on an unrestricted diet was 228 systolic and 109 diastolic, on a diet with a salt content of less than 1 Gm per day, 230 systolic and 104 diastolic, on 10 Gm of sodium chloride per day, 242 systolic and 112 diastolic, on 15 Gm of sodium chloride per day, 236 systolic and 112 diastolic, and on 25 Gm of sodium chloride per day, 237 systolic and 117 diastolic.

CASE 3—F R, a woman, aged 50, was admitted to the hospital on Oct 29, 1923, and was discharged on Dec 17, 1923. The symptoms were throbbing sensations in the head, pains in the abdomen, belching of gas and shortness of breath, all of about four years' duration. The blood pressure at the time of admission was 230 systolic and 115 diastolic. There were no signs of decompensation. The orthodiagram showed the heart to be moderately enlarged to the left and the aorta widened. The urine showed traces of albumin at times and occasional casts. The blood chemistry was normal. The plasma chlorides were 564 mg per hundred cubic centimeters.

With the patient on an unrestricted diet, the blood pressure averaged 201 systolic and 110 diastolic, on a salt intake of less than 2 Gm per day, it averaged 194 systolic and 111 diastolic, and on less than 1 Gm per day, 195 systolic and 112 diastolic.

The patient was readmitted on Jan 7, 1924, and discharged on March 4, 1924. Readmission was due to increase in the symptoms and the presence of fresh retinal hemorrhages. The blood pressure at this time was 264 systolic and 134 diastolic, the blood chemistry was normal and the plasma chlorides were 626 mg per hundred cubic centimeters.

When the patient was on an unrestricted diet, the blood pressure averaged 219 systolic and 117 diastolic, on 10 Gm of sodium chloride per day, it averaged 215 systolic and 111 diastolic, on 20 Gm per day, 225 systolic and 113 diastolic, and on a low salt diet (less than 15 Gm per day), 216 systolic and 117 diastolic

CASE 4—W G, a colored man, aged 49, was admitted to the hospital on May 19, 1923, and was discharged on June 12, 1923. The chief complaints were shortness of breath of six months' duration and swelling of the ankles of three weeks' duration. The blood pressure was 182 systolic and 130 diastolic. The heart was moderately enlarged. The liver was palpable three fingerbreadths below the costal margin, and there was a moderate degree of pretibial edema. The urine showed considerable albumin but no casts. The blood chemistry was normal and the plasma chlorides 597 mg per hundred cubic centimeters

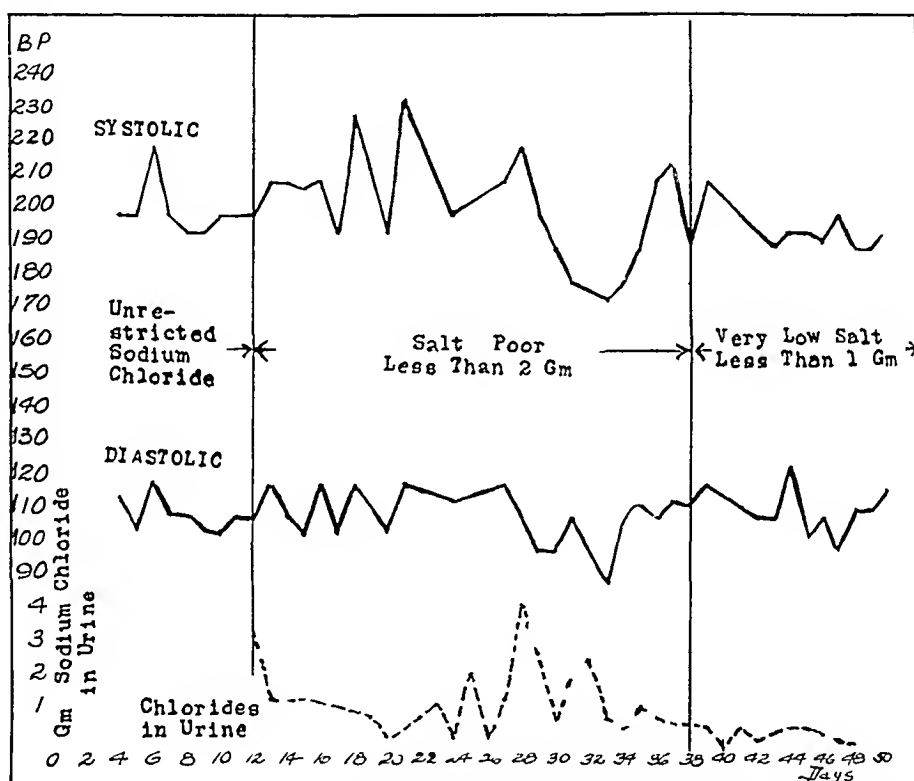


Chart 1—Blood pressure readings, daily chloride output and salt intake in case 3 during the patient's first admission

With the patient on an unrestricted diet, the blood pressure average was 195 systolic and 124 diastolic, and on a low salt intake (less than 0.5 Gm per day) it averaged 190 systolic and 118 diastolic

CASE 5—N W, a woman, aged 43, was admitted to the hospital on March 19, 1923, and was discharged on June 2, 1923. The chief complaints were headaches, backaches, spots before the eyes and frequency of urination. She had known of her hypertension for about two years. The blood pressure was 252 systolic and 130 diastolic. There was slight cardiac enlargement to the left and no signs of decompensation. The blood chemistry was normal, and the plasma chlorides were 582 mg per hundred cubic centimeters. The urine at times showed traces of albumin and occasional casts.

When the patient was on an unrestricted diet, the blood pressure averaged 220 systolic and 115 diastolic, on a low salt intake, 217 systolic and 132 diastolic, on 10 Gm of sodium chloride per day, 201 systolic and 121 diastolic, on 15 Gm of sodium chloride, 204 systolic and 122 diastolic, and on 20 Gm of sodium chloride per day, 203 systolic and 119 diastolic

CASE 6—L K, a woman, aged 40, was admitted to the hospital on May 1, 1922, and was discharged on May 21, 1922. The complaints were chiefly of headaches, and of aches and pains in different parts of the body for about seven years. The blood pressure was 175 systolic and 95 diastolic. There was slight cardiac enlargement, but no signs of decompensation. The blood chemistry was normal. The urine showed slight amounts of albumin at times and occasional hyaline and granular casts.

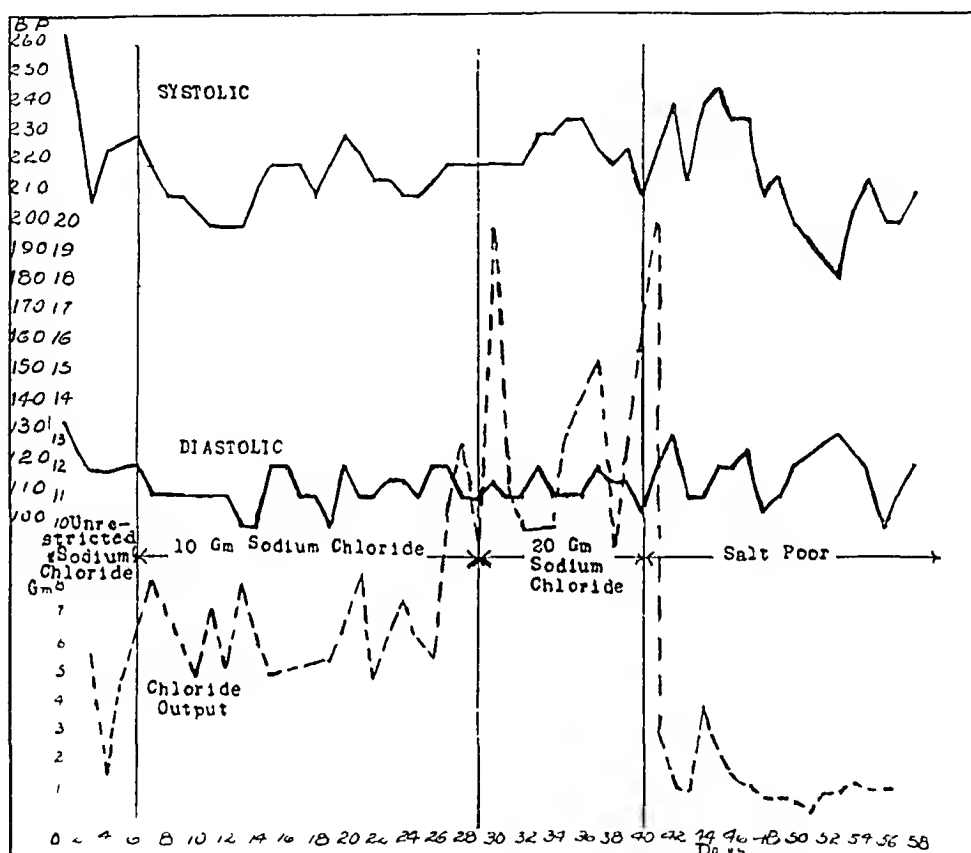


Chart 2—Blood pressure readings, daily chloride output and salt intake in case 3 during the patient's second admission

The blood pressure with the patient on an unrestricted diet averaged 174 systolic and 96 diastolic. On a low salt intake (less than 1 Gm per day) for nine days, the pressure averaged 168 systolic and 98 diastolic. At the end of this period, the patient became so weak (due to salt privation) that she was unable to get out of bed. At this time her urinary chloride excretion was 0.2 Gm per day. Coincidentally with this marked anorexia, the blood pressure fell to 135 systolic and 90 diastolic. The patient was then placed on an intake of 10 Gm of salt per day for nine days, and soon began to show marked improvement. The pressure remained down for about a week, but at the time of discharge it had risen to 175 systolic and 110 diastolic.

The patient was readmitted on Feb 13, 1923, and discharged on March 4, 1923. This time the patient complained chiefly of headaches. The blood pressure at the time of admission was 164 systolic and 90 diastolic. The blood chemistry was normal and the plasma chlorides were 622 mg per hundred cubic centimeters. The urine was normal, except for traces of albumin.

With the patient on an unrestricted diet, the blood pressure averaged 164 systolic and 90 diastolic. On a low salt intake, it averaged 183 systolic and 110 diastolic, and on a very low salt intake, 189 systolic and 110 diastolic.

CASE 7—C W, a man, aged 30, was admitted to the hospital on June 12, 1924, and was discharged on July 23, 1924. The chief complaints were swelling of the legs and generalized weakness of two months' duration. The blood pressure was 150 systolic and 100 diastolic. There was slight edema of the ankles. The urine showed large amounts of albumin and on microscopic examination granular casts. The blood chemistry was normal and the plasma chlorides 597 mg per hundred cubic centimeters.

When the patient was on an unrestricted diet, the blood pressure averaged 152 systolic and 94 diastolic. On a low salt intake (less than 2 Gm per day), it averaged 138 systolic and 98 diastolic, while on a very low salt intake, it averaged 155 systolic and 95 diastolic.

CASE 8—G S, a woman, aged 45, was admitted to the hospital on June 24, 1924, and was discharged on July 12, 1924. The chief complaints were headaches and throbbing sensations of one year's duration. The blood pressure was 200 systolic and 112 diastolic. The orthodiagram showed slight left ventricular enlargement and diffuse aortic widening. There were no signs of decompensation. The blood chemistry was normal, and the plasma chlorides 626 mg per hundred cubic centimeters. The urine contained no albumin, but occasional granular casts were found on microscopic examination.

With the patient on an unrestricted diet, the blood pressure averaged 200 systolic and 112 diastolic. On a very low salt intake, it averaged 158 systolic and 109 diastolic.

CASE 9—S B, a woman, aged 31, was admitted to the hospital on April 7, 1924, and was discharged on May 13, 1924. The chief complaints were shortness of breath, fainting spells and pain in the left side of the chest of three and one-half years' duration. The blood pressure was 190 systolic and 110 diastolic. There were no signs of decompensation. The orthodiagram showed the aorta to be slightly widened and increased in density. The blood chemistry was normal, and the plasma chlorides 586 mg per hundred cubic centimeters. The urine showed small amounts of albumin at times but no casts.

When the patient was on an unrestricted diet, the blood pressure averaged 166 systolic and 98 diastolic. On a very low salt intake (less than 0.5 Gm per day), 155 systolic and 102 diastolic, and on a daily intake of 10 Gm of salt, 148 systolic and 99 diastolic.

CASE 10—E L, a colored woman, was admitted to the hospital on May 6, 1924, and was discharged on June 12, 1924. The chief complaints were frequent severe headaches and occasional fainting spells. The blood pressure was 240 systolic and 120 diastolic. The orthodiagram showed moderate left ventricular enlargement. There were no signs of decompensation. The blood chemistry was normal and the plasma chlorides 577 mg per hundred cubic centimeters. The results of urinalysis were negative.

The blood pressure with the patient on an unrestricted diet averaged 186 systolic and 102 diastolic, on a very low salt intake, 156 systolic and 99 diastolic, and on 10 Gm of salt per day, 182 systolic and 118 diastolic.

CASE 11—E K, a woman, aged 57, was admitted to the hospital on March 9, 1923, and was discharged on June 2, 1923. The chief complaints were shortness of breath, palpitation and precordial pain, as well as generalized aches and pains intermittently for about twelve years. The blood pressure was 240 systolic and 90 diastolic. The oithodiagram showed moderate left ventricular enlargement. The urea nitrogen of the blood was 20 mg per hundred cubic centimeters, and the plasma chlorides 626 mg per hundred cubic centimeters. The urine showed a trace of albumin but no casts. The blood sugar at the time of admission was 184 mg per hundred cubic centimeters, and the first specimen of urine showed a moderate amount of sugar. The diabetes was easily controlled by regulating the diet, and the patient remained "sugar-free" during her stay.

With the patient on an unrestricted salt intake, the blood pressure dropped from 240 systolic and 90 diastolic to 200 systolic and 90 diastolic, but the high

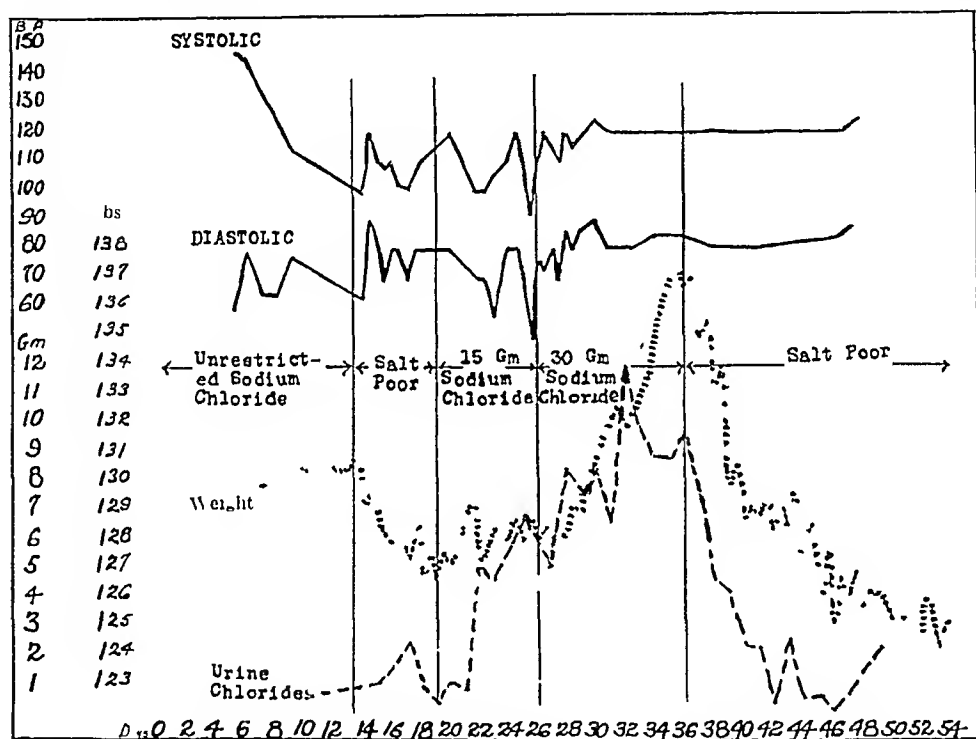


Chart 3—Blood pressure readings, daily chloride output and salt intake in case 12

figures obtained at first served to bring the average pressure for this period up to 221 systolic and 100 diastolic. On a salt intake of less than 1 Gm per day, the pressure averaged 206 systolic and 95 diastolic, and on a high salt intake (reaching an intake at times of 30 Gm per day), it averaged 194 systolic and 91 diastolic.

CASE 12—*Nephrosis*—L R, a man, aged 26, was admitted to the hospital on May 15, 1923, and was discharged on July 7, 1923. The chief complaints were recurrent swelling of the left submaxillary region and swelling of the ankles and legs of about four months' duration. He felt well otherwise. Examination showed slight puffiness of the eyelids and edema of the legs. The remainder of the examination gave negative results. The blood pressure at the time of admission was 146 systolic and 86 diastolic. The blood chemistry was normal. The plasma chlorides were 626 mg per hundred cubic centimeters. The urine

showed large amounts of albumin but no casts, and the specific gravity varied from 1 005 to 1 025. The phenolsulphonphthalein output was 65 per cent in two hours. The eyegrounds were normal.

When the patient was on an unrestricted diet, the blood pressure fell from 146 systolic and 86 diastolic to 115 systolic and 78 diastolic with an average of 136 systolic and 72 diastolic. On a salt-poor diet the pressure then averaged 109 systolic and 77 diastolic. With 15 Gm of salt per day added to the diet, the pressure averaged 109 systolic and 71 diastolic, and with 30 Gm of salt per day added to the diet, 119 systolic and 82 diastolic. Following this the patient was again placed on a salt-poor diet, and the blood pressure averaged 121 systolic and 83 diastolic.

Although the blood pressure was not influenced by the salt intake, careful check on the patient's weight (twice daily weighing) showed that the edema increased with the salt intake.

CASE 13—*Acute Glomerular Nephritis*—J. R., a boy, aged 11, was admitted to the hospital on Nov 20, 1924, and was discharged on Feb 9, 1925. About two weeks before admission the patient had a sore throat. While the patient was

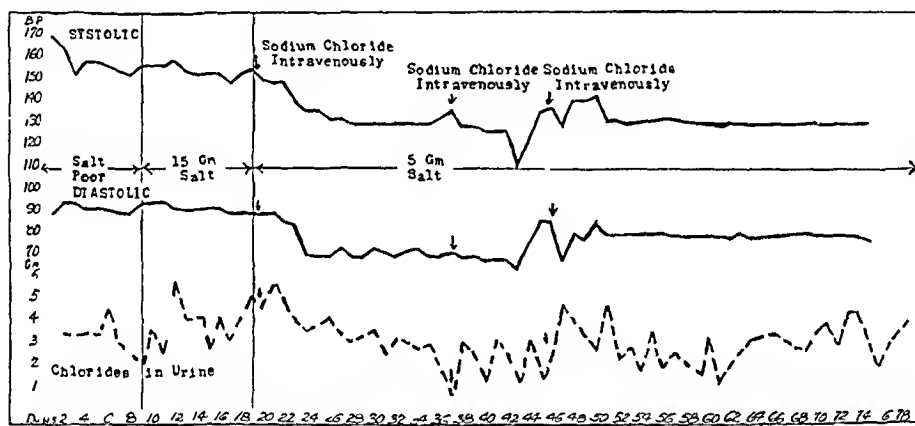


Chart 4—Blood pressure readings, daily chloride output and salt intake in case 13

recovering from this, the mother noticed that the child's face was becoming rather puffy, especially around the eyes. Soon after this the legs also began to swell, and in addition the child began to complain of pain in the back just below the ribs on both sides. Since the onset of his illness, the child had had increased frequency of urination.

Examination showed generalized subcutaneous edema, most marked in the face which was puffy and about the eyes where the swelling was prominent. The tonsils were hypertrophied, and there was some redness of the pharynx. The heart was slightly enlarged. The blood pressure was 170 systolic and 90 diastolic. There was tenderness over both kidneys posteriorly. The urine at the time of admission showed gross blood and a large amount of albumin, and microscopically large numbers of red blood cells, white blood cells and casts. The blood chemistry showed nonprotein nitrogen, 50 mg, urea nitrogen, 23 mg, creatinine 1.6 mg, and plasma chlorides, 530 mg per hundred cubic centimeters.

At the time of admission, the patient was put on a salt-poor diet, following this, 15 Gm of salt per day was added to his diet and later, 5 Gm of salt was added. In addition he was given 5 Gm of sodium chloride (in 5 per cent solu-

tion) intravenously on three occasions. Following the intravenous administration of sodium chloride, the blood pressure readings were taken at hourly intervals, with the results shown in table 2.

The patient improved slowly, and his blood pressure dropped gradually, without regard to the salt intake. At the time of discharge there was no blood in the urine, and the microscopic examination failed to show any red blood cells or casts. Also the edema had entirely disappeared.

#### SUMMARY

1 The effect of sodium chloride on the blood pressure has been studied on eleven patients with so-called essential hypertension, on one patient with nephrosis, and on another with hypertension associated with acute glomerular nephritis.

2 These patients have been carefully observed while on diets containing varying amounts of sodium chloride, ranging from intakes of less than 1 Gm per day to 30 Gm per day.

3 In only one of these cases (case 10) was there an appreciable drop in blood pressure, which seemed to be due to the salt-poor diet.

TABLE 2—*Blood Pressure Readings Before and After the Intravenous Administration of Sodium Chloride*

	Dec 8th	Dec 23th	Jan 4th
Before	164/90	136/72	122/72
1 hour after	150/80	138/70	122/72
2 hours after	162/92	120/66	120/70
3 hours after	160/90	128/70	124/68
4 hours after	160/90	136/72	

4 In another case (case 8) there was a well marked drop in the systolic pressure, but this case was not observed for a sufficient length of time.

5 In a third case (case 6) the blood pressure fell when the patient showed marked signs of salt privation with accompanying anorexia, weakness, etc., but rose again when her condition improved.

6 Reduction of the sodium chloride intake in all of the other cases did not cause a drop in the blood pressure level.

7 Raising of the sodium chloride intake above the normal level also did not have any appreciable effect on the blood pressure.

8 In the patient with nephrosis the edema (but not the blood pressure) varied with the amount of sodium chloride in the diet.

9 Administration of sodium chloride orally and intravenously even to patients with acute hemorrhagic nephritis had no effect on the blood pressure level.

10 The initial level of the plasma chlorides bore no relation to the subsequent course of the case.



## CONCLUSION

Thirteen patients were carefully observed in the hospital for a period of time ranging from twenty to eighty-one days (average, forty-four days). After an initial period of stabilization, rest in bed, diet, etc., ranging from ten to fourteen days, salt was withdrawn from their diet, their output dropping in most instances to below 1 Gm per day and in some as low as 0.5 Gm per day. After they had been kept at this level for periods of from two to five weeks, sodium chloride was added to their diet in quantities of from 10 to 30 Gm per day, supplemented in several instances by the intravenous administration of from 5 to 15 Gm. We have failed to see any unquestioned modification of the blood pressure curve which could be definitely attributed to variations in the sodium chloride intake.

# INTESTINAL OBSTRUCTION AND SEPTIC INVASION OF THE PERITONEUM

COMBINED MEDICAL AND SURGICAL TREATMENT \*

KENNETH PHILLIPS, M D

AND

W PARKER STOWE, M D

MIAMI, FLA

We feel certain that the method which we shall attempt to describe for the control of a definite clinical syndrome has not been described elsewhere. At the same time, we do not claim credit for the origin of the separate and independent factors that are involved in the procedure.

Intestinal obstruction, or at least the clinical picture that we ascribe to it, has been referred to for centuries. Since the etiology, symptomatology and pathology are so well understood and so widely discussed in the literature, we have purposely omitted them from this paper.

Our attention was first directed toward this work several years ago, during a period of physiologic research. At that time the fact which impressed us was that practically all workers were agreed as to the etiology, symptoms and pathology of this clinical picture, but that their differences and difficulties arose in attempting to explain the sequence and the cause of death which followed after the actual obstruction had been produced.

After a careful review of the latest experimental work on intestinal obstruction, peritonitis and ileus, we concluded that the best founded theories today which attempt to explain the clinical syndrome and the cause of death in these conditions rest between those of toxemia, dehydration, perverted secretion, bacteremia, and possibly the most recent of all, advocated by Williams<sup>1</sup> of London, the presence of a toxin due to a specific organism.

We feel that the best founded theory is that of toxemia. One of us was associated with Dragstedt at the University of Chicago when a series of experiments was being carried out in an attempt to produce this clinical syndrome in dogs by means of artificial obstruction.

Since the details of the methods employed, as well as a report of the results, have been so well described and discussed<sup>2</sup> we shall only briefly summarize the work for the sake of giving the basis and beginning of our ideas.

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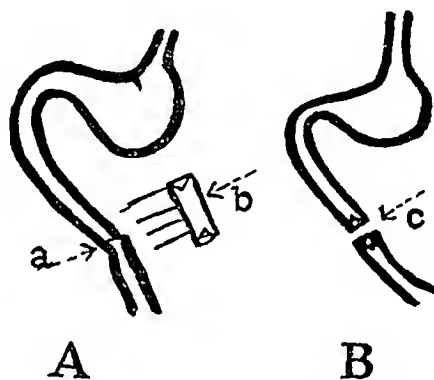
\* Submitted for publication, June 6, 1929

1 Williams, B W. Brit J Surg **14** 295 (Oct) 1926

2 Dragstedt, L R, Moorhead, J J, and Burcky, T W. J Exper Med **25** 421 (March) 1917

After producing artificial obstruction in several different ways, it was the aim of the Chicago workers to produce the same clinical and pathologic picture in their animals and still maintain a patent and, if possible, a functional gastro-intestinal tract. This was accomplished by preparing isolated closed intestinal loops about 12 cm long and reestablishing the tract by end-to-end anastomosis, as shown in *A* in the accompanying illustration.

Both ends of the loop thus isolated were inverted and closed with double rows of purse-string sutures, care being taken not to interfere with the blood supply. The closed loops were then left free in the abdominal cavity. These animals presented a definite and constant train of symptoms, and died in from thirty-six to sixty hours of severe toxemia. The symptom-complex was practically identical with that of the animals in which obstruction had been produced, as shown in *B* in the accompanying illustration, and an autopsy revealed either a



In *A*, the end-to-end anastomosis is shown at *a*, while *b* is the isolated closed loop. In *B*, the bowel is severed, with the free ends closed at *c*.

markedly distended and partially necrotic loop filled with the characteristic reddish-brown, foul-smelling fluid, or a rupture of the loop along the antimesenteric border, with expulsion of the fluid and a general peritonitis.

Further work aimed at the specific nature of this fluid revealed it to be relatively harmless when administered to normal animals by mouth and extremely toxic when given intravenously, its chemical nature seemed to be closely related to the amines, and its origin, in all probability, was from decomposition by the proteolytic strain of intestinal bacteria. Attempts to immunize animals with the material were unsuccessful. During further research on the problem, attempts were made to sterilize the loops previous to closing the ends, in order to control bacterial activity. The various so-called intestinal antiseptics, as well as solutions of phenol compound solution of cresol, mercuric chloride, alcohol and ether, were used. In no case could the loop be sterilized, but with ether and alcohol a retardation of the progress of the toxemia could be effected.

From a careful study of this and other experimental work, we feel that a logical and scientific basis can be set down for the underlying principles in the symptom complex and cause of death in these conditions, and this we feel is always a scientific requirement prior to any treatment that is to be devised, especially if the treatment is to be applied to human beings.

A brief discussion, then, of the most plausible theories is worth while.

Although dehydration did not appear to be an important factor in the animals,<sup>2</sup> we feel that it is a decided factor in cases of clinical obstruction and septic invasion of the peritoneum. We also feel that it is a result of the toxemia and does not play a primary rôle in the morbidity of the patient, since the same end-result can be produced in the cases showing isolated loops, conditions in which there was no excessive vomiting.

It seems unquestionable that there is a perversion of function of the intestinal mucosa in these conditions, but the experimental work would seem to indicate that the perversion has to do with absorption and cellular activity rather than with secretion, since the loops described can be left to drain freely into the peritoneal cavity without any untoward results, also, the fact that in the cases in which the bacterial growth was retarded by removing the substrate from the lumen previous to closing the loops would indicate that the beneficial effect was not on a basis of perverted secretion. A further illustration of this was found in the cases of congenital atresia or other malformations which simulate obstructions, as in an infant in whom the condition was found at birth in our own clinic at the Gowdy Hospital at Miami, Fla., and whose case we reviewed at the time of writing this article and similar cases reported by Long<sup>3</sup> and others. We find that the clinical manifestations do not set in until bacteria enter the tract. Since the glands of the intestinal wall have been active, even before birth, we feel that this also speaks against the theory of a perverted secretion, as advocated by Whipple, Stone and Bernheim.<sup>4</sup>

That a bacteremia is present seems to have been disproved by McClure,<sup>5</sup> McKenna<sup>6</sup> and others,<sup>7</sup> who examined the heart's blood, peritoneum and various organs and found them uniformly sterile.

As to the presence of a specific toxin and the possibility of anti-serum for it, we are waiting for further research.

3 Long, Esmond R. Acute Intestinal Obstruction in a New-Born Infant from Hernia of the Lower Ileum Through a Congenital Mesenteric Opening, *Arch Path* **3** 901 (May) 1927.

4 Whipple, G. H. *J Exper Med* **15** 259, 1912. Whipple, Stone and Bernheim. *Ibid* **17** 286, 1913, *ibid* **19** 144, 1914.

5 McClure, R. D. An Experimental Study of Intestinal Obstruction, *J A M A* **49** 1003 (Sept 21) 1907.

6 McKenna, C. H. *Surg Gynec Obst* **17** 674, 1903.

7 Hartwell, J. H., and Houget, J. P. *Am J M Sc* **143** 357, 1912.

Assuming it to be a well established fact that the first condition following the initial cause in these conditions is a toxemia, we attempted to review other observations on the clinical picture before attempting to rationalize a method of treatment. Probably the most outstanding and valuable of recent contributions have been those of Haden and Orr,<sup>8</sup> who showed the constant changes that occur in blood chemistry. These changes are chiefly an increase in the blood nonprotein nitrogen, a decrease in the chlorides and an increased carbon dioxide-combining power of the blood. These workers advocated, apparently with some success, the intravenous administration of a hypertonic solution of sodium chloride, and other workers<sup>9</sup> confirmed their results and treatment on clinical patients.

A group of workers in Iowa called attention to the lower level of metabolism in these cases. A review of case histories, with regard to symptoms, bears out this suggestion, since many patients manifesting the picture of perforation peritonitis, ruptured viscera or surgical shock, with a metabolic rate that is at a minimum ebb, have been proved, at operation or at necropsy, to have obstruction. The collapse, dehydration and scanty urine would also indicate that both metabolism and excretion are going on at a low level.

Macrae<sup>10</sup> stressed the value of intestinal drainage as a therapeutic measure. Berg, Meloney and Jobling<sup>11</sup> suggested that their work indicated the possibility of the duodenal wall developing an acquired immunity to the intestinal flora, which might even be bactericidal.

During experiments on the function of the duodenum, Dragstedt and his co-workers<sup>12</sup> showed the value of free drainage and frequent irrigations of the duodenum during a partial obstruction. Williams<sup>1</sup> suggested that the toxemia is chiefly caused by anaerobic bacteria and that any means of supplying an excess of free oxygen to the intestinal lumen will aid in combating the gravity of the condition. He developed a serum which we feel has not as yet had a sufficient trial.

During our research and review of the literature on other problems we have found, from time to time, valuable suggestions concerning the problem described in this paper.

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8 Haden, R. L., and Orr, T. G. High Jejunostomy in Intestinal Obstruction, *J. A. M. A.* **87** 632 (Aug. 28) 1926, *J. Exper. Med.* **55** 795, 1926.

9 Coleman, E. P. Use of Hypertonic Saline Solution in Acute Intestinal Obstruction, *J. A. M. A.* **88** 1060 (April 2) 1927.

10 Macrae, Donald, Jr. Management of Acute Conditions of the Abdomen, *J. A. M. A.* **89** 1113 (Oct. 1) 1927.

11 Berg, B. N., Meloney, F. L. and Jobling, J. W. Experimental Chronic Duodenal Obstruction, *Arch. Surg.* **14** 752 (March) 1927.

12 Dragstedt, L. R., Dragstedt, C. A., McClintock, J. T. and Chase, C. S. *Am. J. Physiol.* **46** 584 (Aug.) 1918.

In reviewing the function of the parathyroid glands, Luckhardt,<sup>13</sup> Dragstedt, one of us (K P) and Sudan,<sup>14</sup> Dragstedt and Peacock<sup>15</sup> and Sudan gave vital indications that the tetany following complete extirpation of the glands is intricately related to a toxemia that is most probably concerned with protein split products from the gastrointestinal tract similar in nature to the amines. On this assumption they showed conclusively that these poisonous bodies can be controlled, either at the site of their production by changing the flora and thus the metabolism in the intestine, or after their absorption by copious intravenous injections of physiologic solution of sodium chloride or, preferably, of Ringer's solution. Whether the toxins are free in the blood stream as such, or whether there is some linking up with the cells, which are later broken up, the writers were not able to decide, but improvement in the animals was invariably coincident with violent diuresis.

Fleming<sup>16</sup> showed that the phagocytic power of the leukocytes has a definite relationship to the concentration of salt in the blood, and suggested that with an upset in the concentration of salt the resistance of the blood is temporarily reduced. This is interesting, since there was an upset in salt metabolism in the cases described in this paper.

In thirty-one cases of extensive cutaneous burns, Davidson<sup>17</sup> found that there is a definite fall in the chlorides of both whole blood and plasma, and claimed that in these cases the explanation does not lie in the loss of fluids, the fever, the concentration of blood or the renal threshold, but that the fall appears to be due to disturbed chloride metabolism with retention in the tissues. We feel that this is significant, since it points out a possible relationship to a similar mechanism in toxemias of other origin.

Lipschitz<sup>18</sup> found that after ligation of the pylorus, various substances, including dextrose and sodium salts, when given intravenously would be secreted through the gastric wall into the lumen of the stomach. This might throw some light on the explanation of the loss of chloride in cases of obstruction and is confirmed by the claim of some (Richardson of Boston) that the fluid found in the intestinal lumen, proximal to an obstruction, contains 5 Gm. of chloride per liter.

About three years ago, obstetric literature began to contain reports on the efficacy of the intravenous administration of dextrose and insulin.

13 Luckhardt and Rosenbloom. *Proc Soc Exper Biol & Med* **19** 129, 1921.

14 Dragstedt, L. R., Phillips, K., and Sudan, A. C. *Am J Physiol* **65** 368 and 503, 1923.

15 Dragstedt and Peacock. *Am J Physiol* **64** 424 (May) 1923.

16 Fleming, A. *Brit J Exper Path* **7** 274, 1926.

17 Davidson, E. C. Sodium Chloride Metabolism for Cutaneous Burns and Its Possible Significance for Rational Therapy, *Arch Surg* **13** 262 (Aug.) 1926.

18 Lipschitz, W. *Klin Wchnschr* **5** 2008, 1926.

in treatment for toxemias of pregnancy Dragstedt, one of us (K P) and Sudan,<sup>19</sup> at about the same time, were showing a close and interesting relationship between the toxemias of pregnancy and a syndrome produced artificially in dogs. When a careful scrutiny is made of experimental work on toxemias of pregnancy, acute dilatation of the stomach, parathyroid tetany, peritonitis and the various forms of intestinal stasis and obstructions, one cannot avoid being peculiarly attracted to the evidence of a close relationship between them all, intricately interwoven, and the question arises as to whether there is some basic underlying principle in common. Thus the idea is kept in mind that any successful method of treatment for one condition might well be analyzed and considered in its application to others.

In the routine treatment of patients with tumors of the brain and other intracranial lesions, Kanavel and Davis, of the department of surgery of Wesley Hospital at Chicago, noticed that the intravenous administration of hypertonic solution of dextrose not only gave relief from intracranial pressure but invariably improved the metabolism in general. Holmes and Goldstine, of the medical and gynecologic departments of this hospital, made a similar observation on patients with nephritis and uremia who were being treated with dextrose and insulin, in these patients, a marked diuretic effect was often observed.

#### TREATMENT

On the basis of the aforementioned experimental work, together with clinical reports and observations, we have worked out a combined medical and surgical method of handling these cases of toxemia. The treatment consists of five parts, each of which has its own field and will be discussed later.

Briefly, our method is as follows:

1. A Rehfuess tube is passed into the stomach and the duodenum, where it is left for several days, if necessary, during this period, hourly aspirations, washings and instillations are given.

2. A solution of dextrose in 50 per cent concentration is given intravenously, care being taken to administer it slowly. The amount of each dose will vary from 40 to 100 cc., depending on the size of the patient. At the end of the injection enough insulin to burn this dextrose, calculated on the basis of 1 unit per two grams of dextrose, is given hypodermically.

3. The blood stream is supplied with an excess of fluids which produce better results if given a short time after the dextrose. For this reason we prefer the intravenous method to hypodermochysis in supplying these fluids. We also prefer Ringer's solution to physiologic solution of sodium chloride, but owing to the general unfamiliarity of the medical profession with its use it is customary to use the latter.

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<sup>19</sup> Dragstedt, L. R., Phillips, Kenneth, and Sudan, A. C. *Am J Physiol* 69: 477 (Aug.) 1924.

4 After the diuresis and the effect of the dextrose and saline solution are well under way, an intravenous injection of 10 per cent solution of sodium chloride is given, varying in amount from 75 to 150 cc, according to the size of the patient

5 High enterostomy is performed under local anesthesia in patients who fail to respond to the medical management as well as they are expected to

It will at once be noticed that the treatment is rather generalized. Since every case presents an individual problem in itself, it is impossible to outline the treatment in a definite order. We have had some patients who were moribund and within eight hours we have carried out the entire treatment, including enterostomy, and recovery has occurred. In general, however, we handle our cases in about the order enumerated.

In regard to the number of cases that we have handled, we should like to call attention to the handicap under which we have been working. We are certain that all will agree that clinical research done by those who are not connected with charity institutions is a slow and discouraging process. This work has been done almost entirely on private patients and on patients who have been referred to us by other physicians. Therefore, although our experimental observations began several years ago, we have to date been able to use this method of treatment on only forty patients. We are convinced, nevertheless, that the results are well founded, and during the course of subsequent cases there will be little to add.

#### REPORT OF CASES

We shall limit the cases described to four, which will well serve as examples of the efficacy of our method.

CASE 1—Mrs. A, aged 23, weighing 100 pounds (45.4 Kg), was admitted to the hospital with a condition tentatively diagnosed as pelvic peritonitis. On the second day, the diagnosis was changed to an "emergency case requiring abdominal operation." Laparotomy revealed a diffuse, generalized peritonitis with a greenish-white exudate clinically resembling the pneumococcic type, smears, however, failed to reveal the organisms. There was a deposit of fibrin over the visceral peritoneum, and the loops of the small intestine were kinked and bridged across with fibrin. The loops, which were easily accessible, were freed, and the abdomen was closed with a drain. Twelve hours later, the patient was moribund. The abdomen was markedly distended and rigid. The patient had excruciating pains, a pulse rate of 180 and a temperature of 96.8 F, she was vomiting brown fluid with a fecal odor. A Rehmann tube was passed into the stomach, and 600 cc of brown, foul-odored fluid was aspirated. The stomach was washed and aspirated every half hour with dextrose and saline solutions. The intravenous administration of 40 cc of a 50 per cent solution of dextrose with 20 units of insulin hypodermically was followed by 75 cc of a 10 per cent solution of sodium chloride given intravenously. The patient was symptomatically relieved forty-five minutes after the treatment was completed. The dextrose, insulin and chlorides were given every eight hours for the next twenty-four hours. The patient made a complete recovery. When seen recently, she was feeling entirely well. This case is especially interesting, since clinically the condition seemed to be a pneumococcic peritonitis with recovery.



CASE 2—A boy, aged 12 years, weighing 75 pounds (34 Kg), was operated on for appendicitis. The appendix was purulent and showed beginning gangrene, but there was no perforation. Due to adhesions, a purse-string suture could not be used and the appendix was merely ligated and excised at the base. Immediately after the operation the condition was satisfactory, but in about forty-eight hours the patient began to have excruciating abdominal pain, with visible peristaltic waves followed by vomiting, distention and dehydration. A Rehfuß tube was passed into the duodenum, and 400 cc of brown fluid was aspirated, 1,000 cc of saline solution was given by hypodermoclysis. Hourly aspirations and washings with saline solution and lactose were given. Three intravenous doses of 25 cc of a 50 per cent solution of dextrose, with 10 units of insulin hypodermically, were given, six hours apart. The patient thereupon made a spontaneous recovery. Evidently a kink in the lower ileum had formed in the adhesions, producing an obstruction, and had later straightened out by itself. It is our belief, however, that the medical treatment was responsible for tiding the patient over until the spontaneous recovery took place.

CASE 3—H, a man, aged 35, weighing 145 pounds (65.8 Kg), was admitted with the questionable diagnosis of a perforated viscus. Exploratory laparotomy revealed a markedly distended gallbladder, which was twisted and failed to empty on pressure. The stomach, liver, duodenum and kidneys all appeared to be normal. Cholecystectomy and appendectomy were performed. Immediately after the operation, the condition seemed satisfactory, but six hours later there were severe abdominal cramps, followed by projectile vomiting and marked distention. A Rehfuß tube was inserted, and 700 cc of a yellowish fluid was aspirated. Hourly washings, aspirations and instillations with saline solution and lactose were given. The intravenous injection of 75 cc of dextrose with 20 units of insulin hypodermically was followed by 150 cc of a 10 per cent solution of sodium chloride given intravenously. With the continuous hypodermoclysis of saline solution at the rate of 1,500 cc every twelve or sixteen hours, vomiting ceased and the distention gradually decreased until hardly any was present. Dextrose and chlorides were given every eight hours up to the third day. From the fifth to the eighth day, the patient was given a semisoft diet and retained most of what he ate. On the eighth day he developed severe abdominal pain with some vomiting, but the distention or the fecal odor to the vomitus did not return. The patient manifested symptoms of shock and toxemia and died on the eleventh day. Autopsy revealed a volvulus of the mesentery, with adhesions. A segment of the lower part of the ileum had pushed through the loops in the mesentery, producing a complete obstruction with some gangrene. This case is extremely interesting since at no time was there a diagnosis of organic obstruction on account of the atypical picture and the condition of the gallbladder at laparotomy, still, necropsy revealed a complete obstruction of eleven days' duration, and the treatment had kept the patient alive for that length of time in spite of the obstruction.

CASE 4—Miss G, aged 35, weighing 115 pounds (52.1 Kg), had undergone hysterectomy one year before the present illness. She was taken ill with abdominal pain and vomiting while traveling on the train, and was admitted to the hospital moribund. There was an acetone odor to the breath and 3 plus acetone in the urine, the pulse rate was 160, the respirations 45. Abdominal distention was present, with fecal vomiting. A Rehfuß tube was inserted, and 500 cc of brownish fluid was aspirated. Hourly washings, aspirations and instillations with lactose and saline solution were given, 80 cc of a 50 per cent solution of dextrose was administered intravenously with 20 units of insulin hypodermically, followed by 300 cc of a physiologic solution of sodium chloride intravenously. In six hours,

75 cc of 10 per cent solution of sodium chloride was given intravenously. In twenty-four hours, the patient was much improved, with normal breath and urine. Treatment was continued for another twenty-four hours and a laparotomy performed. This revealed a loop of ileum caught and obstructed in an adhesion, a twist in the mesentery formed a loop through which a second segment of ileum protruded and was obstructed like that in case 3. All who saw this patient agreed that if she had undergone surgical treatment on admission the outcome, in all probability, would have been fatal. Because she was treated before the operation, she made an excellent recovery and has remained well.

#### COMMENT

Just what part the dextrose and insulin play and the mechanism of action are not entirely understood, and experimental work on this particular phase of their action is somewhat lacking. It is known that diuresis is promoted by this method of treatment and is desirable. It has also been established that the intravenous administration of dextrose in hypertonic solutions will withdraw fluids from the tissue cells into the blood stream. Metabolism, at least from a clinical point of view, seems to be stimulated. That the dextrose will furnish some nourishment and energy is definite. But even with this much established, we feel that there is still some mechanism unexplained which contributes to the efficacy of dextrose and insulin in these toxemias. There is considerable suggestion, from the experimental side, that there may be some fixation of these poisonous bodies to the cells. In the presence of insulin it is probably true that the dextrose is oxidized more rapidly, and the process may be thought of as a temporary excess of oxidation of the blood stream. It seems reasonable to suppose that this might play some part in the chemistry of individual cells which might tend to break up a linking or in some other way render the poisonous bodies free in the blood stream where they can subsequently be picked up and handled by Ringer's solution and by the kidneys. At least this much is true. With the administration of dextrose and insulin, the nonprotein nitrogen invariably decreases, without it, the nonprotein nitrogen stays high.

Several workers, especially in Europe, have claimed that after cells are subjected to the intravenous administration of hypertonic solutions of dextrose they have a different susceptibility to radiation. Cramer, Dickens and Dodds<sup>20</sup> showed that cells of normal tissue contain insulin, while those of malignant tissue do not. Warburg claimed that cells of normal tissue oxidize dextrose, while those of malignant tissue split dextrose to form lactic acid. These claims would indicate that the oxidation of dextrose is dependent on the presence of insulin at the site of oxidation. If this is true, there is reason to believe that during the height of these toxemias the cell takes on a pathologic state in which the insulin at the site of oxidation is temporarily bound or rendered

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20 Cramer, Dickens and Dodds. *Brit J Exper Path* 7:299, 1926.

inactive This would also fit in with the clinical observation that dextrose alone does not appear to be as efficacious as when it is combined with insulin

Mueller and the Wieners<sup>21</sup> claimed that the glycogenic function of the liver is increased when insulin is deposited in the skin or other organs This increase is absent when the insulin is given intravenously They concluded that there is a parasympathetic nerve stimulation during the time the insulin exists as a deposit, which is independent of the hormone action present during the time that the insulin is in the circulation If this is true, it is possible that subsequent to the hypodermic deposit of insulin, other functions of the liver, especially those of detoxication and nitrogen metabolism, are increased This theory would fit in with our clinical observation that insulin when given hypodermically appears to be more efficient in these toxemias than when given intravenously

Many other references in the literature contain valuable suggestions as to the action of dextrose and insulin, but further comment seems impracticable within the scope of this paper From the present observations, however, and the study of other work, we feel that in the action of dextrose and insulin in these conditions there is probably some mechanism in the chemistry of individual cells which as yet has not been explained

There have been, especially recently, a group of warm advocates for the intravenous injection of hypertonic saline solution in cases of obstruction The work was probably initiated by Haden and Orr<sup>8</sup> on the basis of the constant fall in chlorides, later, several other favorable reports appeared

In a careful analysis of the entire situation, however, we cannot help but feel that the decrease in chlorides is due to an upset in chloride metabolism plus the loss of chlorides in the fluid secreted into the lumen of the bowel and in vomiting, which has been shown to be 5 Gm per liter, a possible third factor is the toxic bodies A similar decrease in chlorides following cutaneous burns and a similar explanation for it were found by Davidson<sup>17</sup> Lipschitz<sup>18</sup> found secretion of chlorides into the lumen of the stomach after pyloric obstruction Dragstedt and Luckhardt<sup>22</sup> said that the lowered blood calcium in their cases of toxemia occurring after parathyroidectomy was a result of the toxemia If this is true, why is it not possible that the chloride ions are in some way bound or linked at the expense of the blood chloride level? If such reasoning is correct, it is possible that a binding of the chloride ions could set free an excess, so to speak, of the sodium and other positive

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21 Mueller, E F, Wiener, H J, and Wiener, R E Mechanism of Insulin Action, *Arch Int Med* **37** 512 (April) 1926

22 Dragstedt, L R, and Luckhardt, A B *Endocrinology* **8** 657 (Sept) 1924

ions in the blood and thus account, in part at least, for the apparent alkalosis that is present. In brief, we feel that the decrease in the blood chlorides is a result of the toxemia and represents only one part of the picture. A treatment aimed only at restoring the chloride level, while efficacious, is so nevertheless for only one phase of the syndrome.

This theory has been borne out in our clinical patients in whom we have limited the treatment to the intravenous injection of hypertonic salt solution and later have added the other parts of the combined treatment.

We feel that the Rehfuß tube accomplishes three things that are easily explained. First, it serves as a method of at least partial drainage. We have repeatedly aspirated as much as from 700 to 800 cc of a brown, foul-smelling fluid on the initial introduction of the tube, and one hour later one-half as much as at the first aspiration. After slow aspiration until no more fluid returns, the stomach and the dilated bowel can be washed and reaspirated until the return is clear. Dragstedt<sup>12</sup> showed the value of drainage and frequent washings in cases of partial obstruction.

A second use for the Rehfuß tube is to supply food and fluids. At the end of each washing, from 30 to 60 cc of fluid or dextrose solution can be instilled through the tube and left until the subsequent aspiration the following hour. In this connection an interesting and almost constant train of events happens. In the large majority of cases, during the first three or four aspirations the return will be far in excess of the amount instilled one hour previously, even though no fluid could be aspirated before the measured amount was instilled. At about the fourth or fifth aspiration, the amount returned will begin to be less than that instilled one hour previously, and this will continue until no fluid is aspirated and the amount of instillation can be increased. This has happened in patients who later have been proved, at operation, to have complete obstructions in the ileum. Vomiting will almost invariably cease with the first aspiration and washing.

We have already discussed the relationship of the intestinal flora to the formation of toxins and the ability to change the intestinal metabolism by diet as first shown by Kendall<sup>23</sup>. Although the Chicago workers<sup>24</sup> failed to be able to cause an aciduric flora to be retained in the intestine following organic obstruction in a closed abdomen, we feel, nevertheless, that there is a possibility of more successfully accomplishing this if a Rehfuß tube is employed or an enterostomy done, when repeated aspirations and washings are possible. We have therefore recently used lactose solution for instillation and aspiration, while it has

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23 Kendall, A. I. *Gastro-Intestinal Bacteriology*, Philadelphia, Lee & Febiger, 1916.

24 Cannon, Dragstedt and Dragstedt. *J. Infect. Dis.* **27** 139 (Aug.) 1926.

been possible to notice a change in the color, odor and reaction to litmus of the returned intestinal contents, our bacteriologic work is not yet complete and we cannot report the observations at this time

The part played by high enterostomy, we believe, is self-explanatory in some respects, and in others we feel that it is as yet undetermined

Macrae<sup>10</sup> gave excellent comments on the subject, including the technic, and his results are noteworthy In the Rochester (New York) General Hospital, with which one of us (W P S) has been associated, early high enterostomy has proved effective in many cases, especially with the intravenous administration of sodium chloride We believe that high enterostomy has a definite place in the treatment, and in our clinical experience we feel that it has been a factor in saving patients who would not have been saved by our treatment minus this factor It is certainly true that high enterostomy gives a much better and freer method for drainage and washing than the Rehfuß tube Whether or not the admission of free air into the lumen of the intestine plays a definite rôle in the anaerobic metabolism, as suggested by Williams, we are unable as yet to say

Though the continuous vigilance in each case during its entire course, we have found that we are able to determine with pronounced accuracy, when the patient is beginning to fail to respond to the medical treatment as well as expected and at the first manifestation of unfavorable signs we subject him to high enterostomy, under local anesthesia We are convinced from experience that this is early enough, and we are just as emphatic in cautioning against waiting too long In this respect we do not agree with Macrae as to enterostomy done as a routine at the onset of the condition We heartily endorse, however, his opinion regarding the impossibility of draining the abdominal cavity by a small tube through an incision in the skin We are convinced that the medical treatment will suffice in many of the cases, and that enterostomy will thus be unnecessary However, at the first recognition, and early recognition is imperative, that the patient is beginning to lose ground under medical treatment, a high enterostomy should be done under local anesthesia, in the middle of the night, if necessary, for we feel that delay at this point will counteract all that has been gained previously After enterostomy has been performed, we believe that irrigations and instillations with lactose solution are of value

As a brief analysis of our series as a whole, we have attempted to group the forty cases according to etiology Twenty cases were due to paralytic or adynamic ileus and general peritonitis (not including streptococcic invasion), ten to postoperative obstruction, either immediate or late, five to strangulated hernia, two to volvulus, one of which was strangulated, two to carcinoma of the colon, and one to hematogenous peritonitis probably pneumococcic in origin There was a mortality of four cases, or 10 per cent which we feel certain is low

## SUMMARY AND CONCLUSIONS

1 Both experimental and clinical evidence indicates that patients with the various forms of obstruction of the bowel, ileus and septic invasion of the peritoneum, not including streptococcic invasions, all have the underlying factor of toxemia related definitely to protein metabolism within the intestine by bacterial action

2 The evidence indicates that the toxemia is the primary factor following the initial condition, and that the symptoms and changes in the blood chemistry are secondary to it

3 In these patients the condition is usually far advanced by the time they reach the surgeon, and they represent a class of extremely poor surgical risks, if operation is performed immediately, a high mortality rate results. Possibly one exception to this is the cases of strangulation

4 We have shown a combined medical and surgical method of treating these patients which will tide them over until either a spontaneous recovery takes place or, if a laparotomy is required, they are in much better condition for operation, by this method the mortality is greatly reduced. When a diagnosis of strangulation has been made and immediate laparotomy is indicated, we advise giving dextrose and hypertonic saline solution intravenously just prior to the operation

5 The entire mechanism by which dextrose, insulin and hypertonic saline solution act in these cases is not yet understood

6 More bacteriologic investigation is indicated, which we now have in progress

7 We wish to emphasize that there are certain important details in each case that are based almost on intuition rather than on any expressible faculties, and we feel that they are of the utmost importance in helping one to choose just which application to make at the proper time. In the cases of strangulation, surgical intervention within a short time is indicated, but if the intravenous administration of dextrose and saline solution precedes the surgical measures, the patient will be a much better risk and, from our experience, will have a far better convalescence. We believe that our results will be confirmed by those who understand our fundamental basis thoroughly before attempting to use this method

# EFFECTS OF DIATHERMY TREATMENTS ON TEMPERATURE \*

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MINNEAPOLIS

This investigation was carried out to determine the influence of routine diathermy treatments on the general temperature of the patient and on the temperature of the surface of the skin under and adjacent to the electrodes. The temperatures were measured by a thermo-electric method. Copper-advance couples were used. One junction was kept near the body temperature in a thermostat similar to the one described by Clark,<sup>1</sup> with a variation less than 0.02 C. The other junction was placed inside a hypodermic needle and soldered to the point of the needle. The temperatures were determined by means of a galvanometer.

The general temperatures of thirty-two patients receiving routine treatments were studied. A Victor diathermy machine was used. The temperature was recorded at the beginning and at the end of the treatment by placing the variable junction of the thermocouple under the tongue of the patient. The areas treated consisted of the knees, shoulders, ankles, feet and various parts of the back. The duration of treatment varied from fifteen to thirty minutes, the current from 375 to 1,000 milliamperes, and the change in temperature from 0.00 to 0.85 C. The body temperature of most of the patients increased only about 0.10 degree. Patients whose temperatures were below normal at the beginning of treatment experienced the greatest increase. It would be expected that the general temperature should increase the most when large currents were used and when they had a relatively long path through the tissues, also that the rise might be more pronounced the longer the treatment. No such relations were found.

The local surface temperature of twelve patients was studied. For some of these patients the same area was treated on different days and also different areas each day. In this way, the variations in temperature were studied during thirty-eight treatments. In order to measure the change in the local surface temperature, the variable junction of the thermocouple was placed in contact with the skin and beneath the active electrode of the diathermy machine. Some measurements were also

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From the Laboratory of Biophysics, University of Minnesota

1 Clark, Harry. The Measurement of Intravenous Temperatures, *J. Exper. Med.* **35**, 385, 1922

made to determine the relative temperature under different parts of the electrode and on the skin in the immediate vicinity of the electrode. It was found that when there was uniform contact between electrode and skin, the temperature increased the most under the central portion of the electrode and decreased slightly toward the edges of the electrode. Beyond the electrode the temperature increase fell off rapidly and was hardly measurable at a distance of 15 cm. The electrodes consisted of felt (spongiopilin) soaked in a fairly concentrated solution of sodium chloride. The upper surface of the felt was attached to copper gauze which in turn was connected to the diathermy machine by a flexible wire. The size of the electrodes and the current used for the various areas were: for the ankle, a 4 by 8 cm electrode and from 400 to 500 milliamperes current; for the knee, 6 by 10 cm and from 500 to 1,000 milliamperes; for the back and shoulder, 9 by 16 cm and 1,000 milli-

TABLE 1—*Effect of One Diathermy Treatment on Temperature*

Minutes	Temperature, C	Minutes	Temperature, O	Minutes	Temperature, O
0	34.7	12	40.0	24	41.0
1	35.0	13	40.2	25	40.8
2	35.4	14	40.5	26	40.8
3	36.0	15	40.7	27	40.7
4	36.5	16	40.9	28	40.7
5	37.2	17	41.0	29	40.6
6	37.8	18	41.0	30	40.6
7	38.2	19	41.0	31	40.6
8	38.9	20	41.5	32	40.5
9	39.0	21	41.5	33	40.5
10	39.1	22	41.0	34	40.5
11	39.6	23	41.0	35	40.5

\* Position of electrodes in front and rear of right shoulder, position of thermocouple—midpoint of electrode in rear of right shoulder, area treated, 9 by 16 cm, with a current of 1,000 milliamperes.

amperes. The current was applied for from thirty to thirty-five minutes in all treatments referred to in the tables.

Temperature readings were recorded at the beginning and at the end of each minute of treatment. Charts 1 and 2 are typical graphs obtained by plotting the temperature as a function of the duration of treatment. Table 1 gives a detailed record of the effect of one treatment on the temperature. Table 2 gives a summary of the thirty-eight treatments.

The figures show clearly that the temperature increases rapidly at the beginning of the treatment, then more slowly, reaching a maximum from fifteen to thirty minutes after the beginning of the treatment. As a rule, it then falls off slightly and soon reaches a constant value. It was interesting to note that the patient usually started to perspire at the time the maximum temperature was registered. Evidently the cooling effects due to increased circulation of the blood, perspiration and radiation, balanced the heat transferred by the electric current when the constant temperature was reached. From table 2 it can be seen



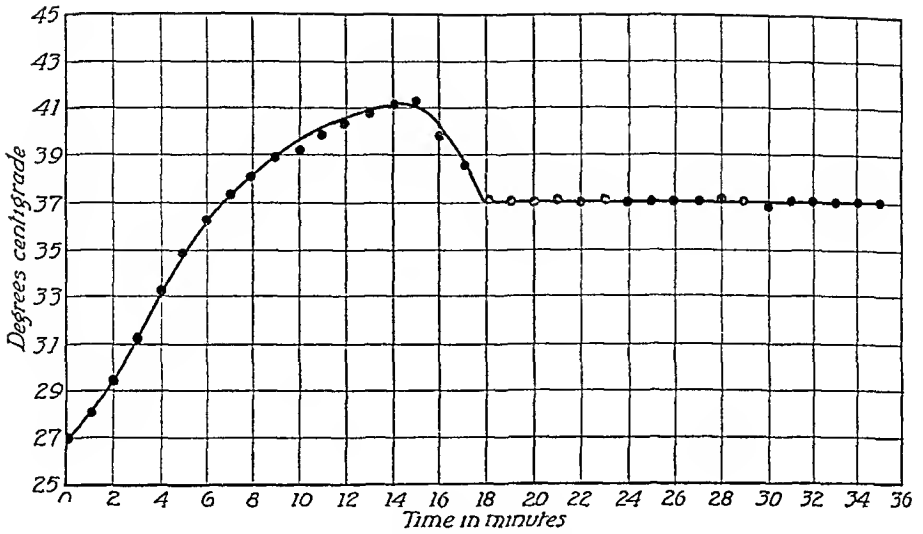


Chart 1—Typical graph obtained by plotting the temperature as a function of the duration of treatment

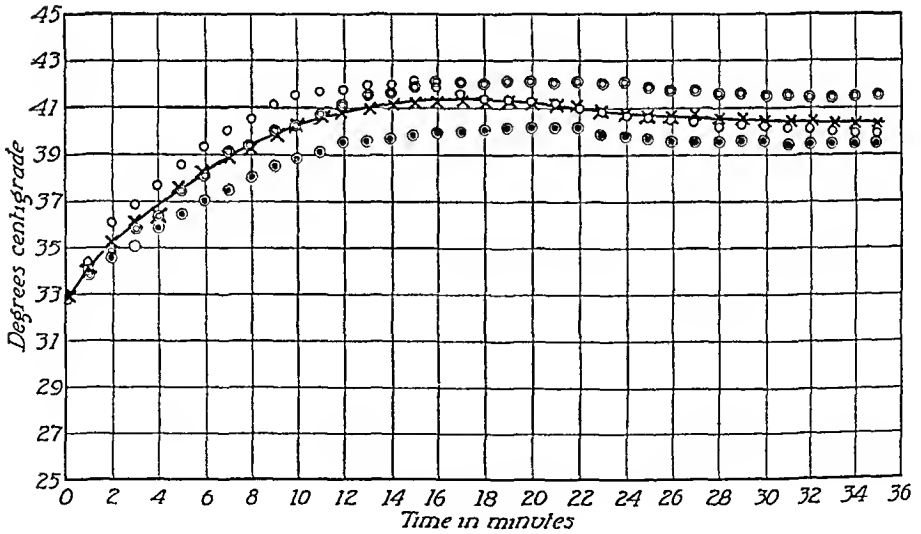


Chart 2—Typical graph obtained by plotting the temperature as a function of the duration of treatment. The white circles indicate the first treatment, the white circles within the white circles indicate the second treatment, the black circles within the white circles, the third treatment, and the x's, the average treatment

that when other factors are about the same, the skin area is heated to a higher temperature when its initial temperature is low than when its initial temperature is higher. This is easy to understand when it is considered that the heat transfer depends on the circulation. The weaker the circulation in the neighborhood the less heat is carried to a surface originally below body temperature and the less heat is carried away from a surface heated above body temperature.

TABLE 2—Summary of Thirty-Eight Treatments

Treatment No	Patient	Location	Current, Milli-amperes	Temperature, C				Minute of Maximum Temperature
				Initial	Final	Maximum	Increase	
1	K B	Right shoulder	1,000	34.7	40.5	41.5	6.8	20
1	M S	Right ankle	400	20.5	32.1	32.1	11.6	30
2	M S	Right ankle	400	23.7	29.2	29.6	5.9	30
2	M S	Left ankle	400	26.3	38.1	38.3	12.0	30
1	M S	Left ankle	400	29.7	36.1	36.2	6.5	25
1	D	Right knee	975	29.0	43.7	44.8	15.8	32
2	D	Right knee	975	30.2	43.0	43.6	13.4	33
2	M H	Right knee	950	20.7	43.0	43.6	22.9	31
1	M H	Right knee	950	27.3	42.4	43.6	16.3	35
3	M H	Right knee	950	28.1	38.3	38.5	10.4	25
3	C B	Right knee	975	30.8	39.7	39.7	8.9	29
1	C B	Right knee	975	31.9	39.0	39.0	7.1	33
2	C B	Right knee	975	32.0	40.4	40.4	8.4	33
1	L W	Right knee	1,000	25.2	42.2	43.9	18.7	17
2	L W	Right knee	1,000	31.3	37.5	37.5	6.2	16
1	L W	Left knee	1,000	27.0	37.0	41.4	14.4	15
3	M S	Left knee	500	24.5	46.8	48.6	24.1	22
5	M S	Left knee	500	26.1	39.7	39.7	13.6	33
2	M S	Left knee	500	28.0	37.7	37.7	9.7	29
4	M S	Left knee	500	29.2	41.0	42.3	13.1	22
1	M S	Left knee	500	29.5	43.6	43.6	14.1	31
3	M S	Right knee	500	24.4	44.5	44.7	20.3	20
5	M S	Right knee	500	25.8	43.7	44.2	18.4	25
1	M S	Right knee	500	27.5	42.9	44.2	16.7	14
2	M S	Right knee	500	28.3	37.0	37.0	8.7	31
4	M S	Right knee	500	30.0	38.9	29.5	9.5	27
1	W	Right knee	750	28.0	41.6	41.9	13.9	26
1	W	Right knee	750	29.5	45.5	46.2	16.7	14
2	H N	Left knee	850	24.5	41.6	41.7	17.2	24
3	H N	Left knee	850	25.7	41.2	41.2	15.5	27
1	H N	Left knee	850	28.0	36.1	36.1	8.1	33
1	K B	Right ankle	500	27.7	40.1	40.6	12.9	27
2	K B	Right ankle	500	29.8	39.7	39.8	10.0	31
1	M K	Back	1,000	32.4	39.9	41.9	9.5	13
2	M K	Back	1,000	33.0	41.5	42.1	9.1	19
3	M K	Back	1,000	33.4	40.0	40.3	6.9	21
1	M F	Back	1,000	33.7	40.7	41.0	7.3	22
2	M F	Back	1,000	33.7	40.9	41.2	7.5	23

## CONCLUSIONS

- 1 The center of the electrode is the point of highest temperature.
- 2 The diathermy treatments given produced little effect on the general temperature of patients whose general temperatures are normal at the beginning of the treatment.
- 3 In most cases observed, a maximum surface temperature was reached between the twentieth and thirtieth minute of treatment.
- 4 An area having a relatively low surface temperature at the beginning of treatment undergoes a greater increase in temperature than does one having a more normal temperature at the beginning of the treatment.

# MENINGO-ENCEPHALITIS DUE TO *TORULA* HISTOLYTICA \*

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AND

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The literature on the comparatively rare condition called meningo-encephalitis contains descriptions of eighteen authentic cases of *Torula* infection. The subject was thoroughly reviewed in 1916 by Stoddard and Cutler,<sup>1</sup> in 1924 by Sheppe - and in 1925 by Shapiro and Neal.<sup>3</sup> A great many cases in the past must have simulated tuberculous meningitis, tumor of the brain or epidemic encephalitis. The cases shown in table 1 have been regarded as true instances of torulosis confirmed by culture and (or) tissue studies. An additional instance of the infection is added to the literature in the case herewith reported.

Fourteen of the nineteen cases involved the central nervous system, two, the central nervous system and lungs, one, the lumbar muscles and vertebral column, one, the pelvic and inguinal tissues, and one, the lungs. All cases involving the central nervous system have resulted fatally. The youngest patient in the series was 13 years and the oldest 57. The cases have been widely distributed. Including the patient whose case is reported, seven of the nineteen patients were from California.<sup>4</sup>

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\* Read before the Los Angeles County Medical Association, April 18, 1929.

1 Stoddard, J. L., and Cutler, E. C. Monogr. Rockefeller Inst. Med. Research, 1916, no. 6.

2 Sheppe, W. M. Am. J. M. Sc. **167** 91, 1924.

3 Shapiro, L. L., and Neal, J. B. Torula Meningitis, Arch. Neurol. & Psychiat. **13** 174 (Feb.) 1925.

4 To these eighteen cases should possibly be added the case reported by G. H. Hansmann (Boston M. & S. J. **190** 917, 1924) in which tuberculous meningitis was considered the cause of death at autopsy of a man, aged 45. Subsequent microscopic examination of sections from the meninges showed an organizing exudate characterized by newly formed fibrous tissue which contained many giant, endothelial, lymphoid and plasma cells, and areas of necrosis. In the lesion, yeastlike organisms were found, many of which were included in giant cells. It was mentioned that the necrotic areas contained many polymorphonuclear leukocytes. In oidiomycosis polymorphonuclear leukocytes are commonly found in the exudate. In torulosis such observations are uncommon. Cultural studies were not made. Likewise, the case reported by C. A. McKendree and L. H. Cornwall (Meningo-Encephalitis Due to *Torula*, Arch. Neurol. & Psychiat. **16** 167 [Aug.] 1926) should probably be included because of the clinical and microscopic observations. Their patient was a woman, aged 50. Yeastlike

## CLASSIFICATION OF THE BLASTOMYCETES

*Torula*, *Oidium* and *Monilia* have been classified as fungi imperfecti under the group *Blastomycetes*. These organisms include *Monilia psilosis*, believed by Ashford to bear an etiologic relation to spue, *Oidium*, identified by Gilchrist<sup>5</sup> as a cause of parasitic dermatitis, *Oidium albicans* present in the parasitic stomatitis known as thrush, as well as other varieties of *Oidia* present in systemic invasions, and *Torula* (table 2).

Stoddard and Cutler were the first to differentiate the lesions produced by *Torulæ* and *Oidia*. These organisms differ from the true yeasts (*Saccharomyces*) in the constant absence of endospore production and their more marked pathogenicity for animals. Stoddard and Cutler have stated that the true yeasts are but feebly pathogenic for animals, and that to 1916 there were but two authentic infections in man, both of which included lesions of the skin. It is possible that some of the cases reported by Breed<sup>6</sup> were instances of such infection. The organism which was identified by her as *Saccharomycete* was pathogenic for mice, rabbits, guinea-pigs and monkeys. The organism was obtained from the sputum of two patients with obscure conditions of the lungs.

The first spontaneous case of torula infection was described by Frothingham<sup>7</sup> in 1902 and occurred in a horse. *Torulæ* are widely

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cells were found in the spinal fluid, but were at first believed to be a contamination. A second specimen of spinal fluid was not obtained as the patient left the hospital. The duration of the illness was about seven and one-half months. Only the brain was examined after death. Their studies led to the conclusion that the cause of death was a progressive meningo-encephalitis due to *Torula*. To these cases should be added the one reported by B. Z. Rappaport and B. Kaplan (Generalized *Torula* Mycosis, Arch. Path. 1:720 [May] 1926). Their patient was a man, aged 54, whose illness covered a period of from four to six months. Four spinal fluid cultures contained yeastlike organisms. Four blood cultures likewise contained pure cultures of similar organisms. Cultures from the nasopharynx and from an indurated crusted papule on the forehead also contained the same yeastlike organisms. At autopsy lesions were found in the central nervous system and lung. They concluded that the meningitis due to *Torula* possibly originated from a sphenoidal sinusitis which was followed by a generalized torulosis including many organs. After the death of the patient they obtained, in addition, cultures of oidium-like organisms from the spinal fluid, the sphenoid sinus, the temporal fossa, the suprarenals, from an abscess in a pulmonary lobe and from the bone marrow. Repeated attempts to isolate torula organisms were made without success. They have suggested the possibility that the postmortem strains were mutation strains of those found before death, or that the postmortem strains overgrew the antemortem organisms.

5 Gilchrist, T. C. Johns Hopkins Hosp. Rep. 1:269, 1896.

6 Breed, L. M. Further Observations with a *Saccharomyces*. J. A. M. A. 61:472 (Aug. 16) 1913.

7 Frothingham, L. J. M. Research 8:31, 1902.

distributed in nature. They have been found in the earth, in the nests of insects and on trees and fruits. A number of varieties have been described. *Toxulæ* multiply by budding, and do not produce endospores,

TABLE 1—True Instances of *Toxulosis*

	Number of Cases	Sex	Age	Race	Organs Chiefly Involved	Diag- nosis Made	Duration of Disease, Months	Result
Von Hansemann Verhandl d deutsch path Gessel sch 9 21, 1906	1	M	18	German	Central nervous system	Post mortem		Fatal
Turek, W., Arch f klin Med 90 335, 1907	1	F	43	Austrian	Central nervous system	Post- mortem	1½	Fatal
Brewer, G. E., and Wood, F. C. Ann Surg 48 889, 1908	1	M	20	Russian (New York)	Abscess of lumbar muscle and vertebral column	By cul- ture	5	Recovered
Rusk, G. Y. Univ Calif Pub Path 2 47, 1912	1	M	57	German (California)	Central nervous system	Post- mortem	About 10	Fatal
Rusk, G. Y. Univ Calif Pub Path 2 47, 1912	1			German (California)	Central nervous system	Post- mortem	1	Fatal
Stoddard and Cutler <sup>1</sup>	1	F	42	American (Florida)	Central nervous system	Post mortem	3½	Fatal
Stoddard and Cutler <sup>1</sup>	1	M	39	American (Massachu- setts)	Central nervous system	Post mortem	3	Fatal
Pearson P. H. J. A. M. A. 69 2179 (Dec 29) 1917	1	M	57	American (California)	Central nervous system	Post mortem	1½	Fatal
Evans, N. California State J Med 20 383, 1922	1	M	13	Mexican (California)	Central nervous system	Ante mortem	1¼	Fatal
Evans, N. California State J Med 20 383, 1922	1	F	20	Mexican (California)	Central nervous system	Ante mortem	2¼	Fatal
Bettin, M. E. California & West Med 22 98, 1924	1	F	40	American (California)	Central nervous system	Ante mortem	1¼	Fatal
Freeman, W., and Weid- man, F. Arch Neurol & Psychiat 9 589 (May) 1923	1	M	39	American (Pennsyl- vania)	Central nervous system	Ante mortem	4	Fatal
Sheppe <sup>2</sup>	1	M	48	American (Virginia)	Lungs	Post mortem	6	Fatal
Shapiro and Neal <sup>3</sup>	1	M	16	American (New York)	Central nervous system	Ante- mortem	7	Fatal
McGehee, J. L., and Michel- son, I. D. Surg Gynec Obst 42 803, 1926	1	F	26	African (Tennessee)	Inguinal abscess	By cul- ture	6¼	Recovered
Lynch, F. B., and Rose, E. Am J Clin Med 4 755 1926	1	M	46	Jewish (Pennsyl- vania)	Central nervous system	Ante mortem	5	Fatal
Hall, G. W., Hirsch, E. F., and Mock, H. Arch Neurol & Psychiat 19 689 (April) 1928	1	M	33	American (Illinois)	Central nervous system	Ante mortem	1	Fatal
Hirsch, E. F., and Gole- man, G. H. J. A. M. A. 92 437 (Feb 9) 1929	1	F	30	African (Illinois)	Lungs central nervous system	Ante mortem	5	Fatal

fermentation of the sugars or mycelia in tissue or in culture. *Oidia* likewise multiply by budding and do not produce endospores, but they do produce fermentation of the sugars, and mycelia are developed in culture. The staining characteristics have been described as follows

*Torula* cells stain diffusely with methylene blue (methylthionine chloride, U S P ) or hematoxylin, while oidia cells are not readily stained by these dyes. The cell products of *Torula* are of gelatinous consistency and the exudate partakes of this quality. It was this characteristic that prompted Stoddard and Cutler to suggest the name *Torula histolytica*.

It is safe to conclude that cultural criteria have not been followed in many cases reported as systemic blastomycosis, with the result that some of the instances so reported may have been due to *Torula*. It may be more academic than useful to attempt such differentiation in a comparatively rare condition. In the interest of accurate nomenclature it will be of value if differentiation by culture studies is used in future reports, at least until more information is available. Such differentiation may not always be possible, as happened in the case described by Rappaport and Kaplan. More than forty cases of systemic blastomycosis, or oidio-

TABLE 2—Classification of the Blastomycetes \*

Fungi	Schizomycetes (fission fungi)	Bacteriaceae (bacteria)			
	Eumycetes (true fungi)	Phycomycetes (algal fungi)	Aseomycetes	Saccharomycetes (true yeasts)	Endospore formation
		Myxomycetes (blastomycetes)	Basidiomycetes	Coccidioides immitis	
			Fungi imperfecti	Torula Oidium Monilia Dematium	No endospore formation

\* This classification has been slightly modified from that given by Sheppe, which was based on the publications of Klocker (Fermentative Organisms, New York, Longmans, Green & Co., 1903) and Weis (J M Research 7 280, 1902), with modifications suggested by I F Lewis of the Department of Biology, University of Virginia.

mycosis, have been reported. Many more instances of local cutaneous lesions produced by *Oidia* have been reported. These include the cases described by Eisendrath and Ormsby,<sup>8</sup> Krost, Moes and Stober,<sup>9</sup> Bechtel and LeCount,<sup>10</sup> Riley and LeCount,<sup>11</sup> Lewison and Jackson,<sup>12</sup> Myers and Stober<sup>13</sup> and Wilhelmj.<sup>14</sup>

8 Eisendrath, D N, and Ormsby, O S. A Case of Systemic Blastomycosis, with Blastomycetes in the Sputum, J A M A 45 1045 (Oct 7) 1905

9 Krost, R A, Moes, M J, and Stober, A M. A Case of Systemic Blastomycosis, J A M A 50 184 (Jan 18) 1908

10 Bechtel, R E, and LeCount, E R. A Case of Systemic Blastomycosis with Necropsy, Arch Int Med 13 609 (April) 1914

11 Riley, F B, and LeCount, E R. A Case of Systemic Blastomycosis, Arch Int Med 13 614 (April) 1914

12 Lewison, M, and Jackson, H. A Case of Systemic Blastomycosis, Arch Int Med 13 575 (April) 1914

13 Myers, H J, and Stober, A M. A Case of Systemic Blastomycosis, Arch Int Med 13 585 (April) 1914

14 Wilhelmj, C M. Am J M Sc 167 91, 1924

## CLINICAL ASPECTS OF TORULOSIS AND OIDIOMYCOSIS

Aside from the cultural differences, oidiomycosis has been found to differ clinically from torulosis in several ways which are not always characteristic. In torulosis the organisms have been found to have predilection for the central nervous system and lungs, although the liver, spleen and kidneys may also be affected. The skin or bones have rarely been involved. The clinical course has been characterized by chronicity with moderate fever and slight leukocytosis. Pathologically, nodules composed of giant and epithelioid or lymphoid cells have been found. Polymorphonuclear leukocytes have not been found in the nodules or the exudate. When caseation has been found, it has been believed to have resulted from the lytic action of the organisms or their products. *Torula* infection has shown marked pathogenicity for mice and rats, while rabbits, guinea-pigs and dogs have been only slightly susceptible. When intraperitoneal injections are made into animals, the lesions have been found to involve the meninges and brain, lungs, liver and spleen. The peritoneum has been but slightly involved. No known therapeutic agent has been found of value in treatment.

In oidiomycosis the lesions have been found to involve the skin and bones, but they may involve all organs. The lesions have been found to consist of nodules with or without caseation and of superficial or deep abscesses which contained many polymorphonuclear leukocytes. The cell products or exudate does not partake of a gelatinous consistency. The organism has been found but slightly pathogenic for all experimental animals. When intraperitoneal inoculation has been made, a marked local peritoneal reaction has occurred. While other organs may be involved, the central nervous system has usually been spared. The iodides have been found of value in treatment.

## REPORT OF CASE

*History*—H. S. McG., a surgeon on the staff of the Pasadena Hospital, aged 51, consulted Dr. Roy R. Miller on Jan. 10, 1929, because of intermittent headache of about one week's duration. In 1920, he had an attack of right frontal sinusitis which was relieved by an intranasal operation. At the time of examination there was no fever, and the pulse rate was 64. In the region of the right middle meatus, scar tissue was evident from the earlier removal of the anterior portion of the middle turbinate. In the left nares a small polyp arising from an anterior ethmoid cell was seen beneath the middle turbinate. Farther back between the middle turbinate and the septum was a larger polyp which obstructed the view of the anterior sphenoidal wall. The frontal sinuses and antrums transilluminated well. The roentgenologic interpretation of films of the nasal sinuses pointed to the presence of a chronic infection of the left ethmoid sinus and the right maxillary sinus (Dr. Carl Parker). The lower second bicuspid was a nonvital tooth, but the roentgenograms revealed no recognizable changes at the apex, and it was believed that the teeth were not a probable source of infection. The urine was normal. On January 17, with the patient under local anesthesia, the two polyps in

the left nares were removed. Examinations with the nasopharyngoscope revealed that the larger polyp originated in a posterior ethmoid cell. The left anterior sphenoidal wall appeared normal, as did also the right posterior ethmoid area and the right sphenoidal wall. The ocular fundi were normal. The headache was not relieved by the removal of the polyps.

*Examination*—The patient was examined by Dr. Stone on January 22. The headache was occipital and intermittent. There was an absence of rigidity of the neck, nausea and Kernig's sign. The temperature was normal. A faint trace of albumin was present in the urine. The leukocyte count was 7,850 per cubic millimeter, of which 67 per cent were polymorphonuclear cells. The blood pressure was 145 systolic and 90 diastolic, and the heart tones and rhythm were normal. The heart rate was 64. The pupils were slightly larger than normal, but reacted to light and in accommodation. The fundi were normal. During the next week, he complained of more or less constant pain in the lower cervical and dorsal spine, and slight fever (from 99.6 to 100.2 F) occurred on two or three occasions. Roentgenograms of the spine showed chronic hypertrophic arthritis of the dorsal vertebrae (Dr. John Chapman). On January 24, the chemical analysis of the blood showed nonprotein nitrogen, 40 mg, creatinine, 1.3 mg, and sugar, 125 mg per hundred cubic centimeters. Examination of the blood showed hemoglobin, 85 per cent (Hellige), red cells, 6,096,000, and leukocytes 11,800 per cubic millimeter, the polymorphonuclear cells numbered 78 per cent, and the lymphocytes, 16 per cent. On January 29, the urinalysis showed that the urine was normal, and the leukocytes numbered 10,600 per cubic millimeter. Examination of the lungs revealed no gross changes. On January 30, the neck became slightly rigid, the right pupil was slightly dilated, Kernig's sign was positive and the right patellar reflex was absent. Dr. William Edler detected paresis of the left facial muscles, and the abdominal and cremasteric reflexes were diminished.

*Course of Illness*—The patient entered the hospital on January 31, and a tentative diagnosis of encephalitis or meningitis type undetermined was made. At the time of admission, the blood count showed hemoglobin, 83 per cent (Newcomer), red cells, 4,450,000, leukocytes, 8,500 per cubic millimeter, and polymorphonuclear cells, 68 per cent. The spinal fluid was under increased tension (from plus 20 to 22 mm of mercury) and showed an average cell count of 300 per cubic millimeter, of which 97 per cent were reported as lymphocytes. The spinal fluid showed a heavy trace of globulin, the sugar content was 27.2 mg per hundred cubic centimeters, and the Wassermann reaction was negative. The smear revealed numerous budding cells resembling *Torula*.

During his first week in the hospital, the patient complained of pain in the head and neck. He was irrational at times, but was able to take food. There was no nausea or vomiting. The temperature varied between 98.6 and 101 F and the pulse rate from 68 to 80. He complained of dimness of vision on the third day in the hospital. Lumbar puncture was done twice daily, for purposes of drainage, in amounts varying from 30 to 50 cc during his three weeks in the hospital. All specimens contained *Torulae*. The fluid was slightly turbid. The pupils were widely dilated at intervals and he did not recognize light, although he recognized the voices of his family and friends. Dr. Miller's examination revealed absence of paresis of the external eye muscles. The retinal veins were moderately distended, but no definite blurring of the borders of the disks was evident. Nasal cultures showed *Staphylococcus aureus* and *albus*. The blood cultures were negative after seventy-two hours' incubation. Involuntary evacuations of the bladder and rectum occurred. The leukocyte count was 12,000 per cubic millimeter five days after admission, and the polymorphonuclear cells numbered 82 per cent.



During the second week in the hospital, the patient was more stuporous. The pupils became smaller and he was less restless after the lumbar punctures. Profuse perspiration occurred at intervals. Weakness of the right hand was evident. The pulse rate gradually increased from 100 to 120 per minute. The temperature varied between 101 and 102 F.

During the third week in the hospital, hiccupping occurred more or less constantly for six days. The rigidity of the neck was marked but opisthotonos was absent. The coma became deeper, the respirations increased to 60 per minute, the rectal temperature rose to 108 F, and death occurred on February 21, 1929. The total duration of the illness, which began with headache about January 6, was seven and one-half weeks.

*Treatment*—It was suggested by Dr. Carl Rand that hexamethylenamin administered intravenously be given therapeutic trial. He had used the drug extensively in his surgical service at the Los Angeles General Hospital in the treatment for meningitis following fractures of the skull. It was given intravenously in doses of 2 Gm, usually three times daily, for thirty-one doses or a total of 62 Gm. Tests of the spinal fluid for the presence of formaldehyde were made daily, with the use of the phloroglucin reagent<sup>15</sup>. Of twenty-four specimens of spinal fluid so examined, formaldehyde was found in four. The *Toxula* cells appeared to diminish in number in the spinal fluid, but were never absent. The use of the reagent was attended by severe discomfort of the bladder and strangury at times. It appeared to have no effect on the progress of the infection.

Experiments were performed with gold sodium thiosulphate, which was added in a dilution of 1:2,000,000 to a proved culture of *Toxula* in broth, and to a culture of *Toxula* in broth obtained from the spinal fluid of the patient. At the end of twenty-four hours, examination showed an average of one budding cell to a high power field, while in the control tubes, without gold sodium thiosulphate, an average of ten budding cells was seen per high power field. Because of its apparent inhibitory action on *Toxula* in vitro, gold sodium thiosulphate in four doses, of from 40 to 50 mg each dissolved in 5 cc of sterile distilled water, was given intravenously at intervals of three days. A positive reaction for a gold compound was obtained in the blood twelve hours after the intravenous injections, and the spinal fluid was tinged yellow. The spinal fluid on only one occasion gave a strong positive reaction for the gold compound.

Following the suggestion of Dr. H. P. Jacobson of Los Angeles, who had used colloidal copper in the treatment for coccidioidal granuloma, experiments were also performed with colloidal copper, iodized poppy-seed oil and ethyl diiodobromide plus iodine. The inhibitory action of the colloidal copper, in dilutions from 1:500,000 to 1:2,000,000 added to broth cultures, was negligible. *Toxulae* seemed to grow as well in dilutions of colloidal copper as in plain broth. Definite inhibition occurred in the dextrose broth cultures to which iodized oil had been added. In control broth cultures, the growth was approximately fifty times more profuse after forty-eight hours than in iodized oil. Cultures made in ethyl diiodobromide plus iodine showed marked inhibition of growth. Cultures made in ethyl diiodobromide plus broth were unsatisfactory, since the ethyl diiodobromide did not mix well with the mediums.

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15 Phloroglucin, chemically pure, 1, sodium hydrate, chemically pure, 20, distilled water, sufficient to make 100 cc. The test was performed as follows: 5 cc of spinal fluid was placed in a tube and 1 cc of the reagent was placed by a pipet so as to form a zone of contact beneath the spinal fluid. A purple tinge changing to pink indicated the presence of formaldehyde.

The following roentgen experiments were performed by Dr John Chapman of the x-ray department of the Pasadena Hospital. Two cultures of *Torula*, one freshly inoculated in spinal fluid and one twenty-four hours old in dextrose broth, were placed inside of a skull and surrounded by bags of a density approximating that of soft tissue. Exposures to the roentgen rays approximating a one-fourth erythema dose were given as follows: 200 kilovolts, 30 milliamperes, through 0.5 mm of copper, 1 mm of aluminum and 2 cm of wood as filters, distance 80 cm, time eight minutes. The roentgen exposures had an apparent inhibitory action on the growth of the *Torula* cultures at the end of eighteen hours, and transplants showed no growth after twenty-four, forty-eight and seventy-two hours. On February 10, the patient received deep roentgen therapy over the posterior surface of the head, with the dosage mentioned, for eight minutes. On February 11 the same treatment was given over the cervical and the dorsal spine.

The following experiments were performed with gentian violet because of its known inhibitory effects on other gram-positive organisms. In a dilution of 1:25,000, very noticeable inhibition of *Torula* growth was evident in eighteen hours. At the end of seventy-two hours, moderate inhibition of growth was evident in

TABLE 3—*Fermentation Reactions*

	Known Culture, <i>Torula histolytica</i> *			Culture Under Investigation		
	Acid	Fading to No Acid	Gas	Acid	Fading to No Acid	Gas
Lactose	No	No	No	No	No	No
Saccharose	Yes	Yes	No	No	No	No
Maltose	Yes	No	No	No	No	No
Mannite	Yes	Yes	No	No	No	No
Dextrose	Yes	Yes	No	Yes	No	No
Galactose	Yes	Yes	No	Yes	Yes	No
Levulose	Yes	No	No	Yes	No	No

\* The known culture of *Torula histolytica*, isolated from a case of torula meningitis in 1920 (Evans, California State J Med **20**: 383, 1922), was obtained from the American Type Culture Collection, John McCormick Institute for Infectious Diseases, Chicago.

the culture which contained gentian violet in a dilution of 1:50,000. On February 16, an injection of 20 cc of gentian violet solution (0.5 per cent) was given intravenously. On February 17, after spinal drainage, 0.5 cc of 1 per cent gentian violet solution was mixed with 10 cc of spinal fluid and allowed to flow into the spinal canal by gravity. Eight hours later, after spinal drainage, 1 cc of 1 per cent gentian violet solution was mixed with 10 cc of spinal fluid and allowed to flow in by gravity. On February 18 and 19, the same procedure was followed, 1.5 cc of 1 per cent gentian violet solution mixed with 10 cc of spinal fluid being used. There was no marked diminution of *Torulae* in the spinal fluid withdrawn after these treatments.

*Cultural Characteristics*—Primary cultures of the yeastlike organisms obtained on numerous occasions from the spinal fluid grew well on all culture mediums. The best growth was obtained on Loeffler's blood serum and in 1 per cent dextrose broth. The growth was present in from thirty-six to forty-eight hours, and appeared on solid mediums as fine, white, granular and slightly raised colonies which coalesced and produced a light yellow pigmentation. A growth was obtained at both 37 C and at room temperature. The best results were obtained by starting the growth in the incubator for from four to six hours and then by removing it from incubator to room temperature. In the tubes of dextrose broth, the growth occurred at the bottom of the tube, and later appeared as a scumlike growth on the surface of the broth.

*Morphologic Characteristics*—The organism was round, with a cell wall of single or double contour, the internal protoplasmic mass frequently being granular. Reproduction occurred by budding, which often took place in chains of from four to six buds. No definite mycelium was produced, but in old cultures hypha-like tube buds were frequently found. No ascospores were demonstrated.



Fig 1—Cut section of consolidated area at the apex of the right lung

*Staining and Fermentation Properties*—The organism stained readily with all the usual stains, and was consistently gram-positive. The organism produced acid but no gas on dextrose, galactose and levulose, the acid fading to no acid on galactose. Lactose, saccharose, maltose and mannite showed no changes (table 3).

*Classification*—The organism was identified as *Torula histolytica* (Stoddard and Cutler) or by Castellani's classification as *Cryptococcus histolytica*.

*Autopsy Observations*—The calvarium was normal. The brain was removed and hardened in 4 per cent formaldehyde solution. The dura was adherent by fine, reddish, granular and dense fibrinous adhesions. The vessels were moderately injected and over the base and cerebellum were stained a light purple. A thin, white, granular exudate covered the entire surface of the brain and infiltrated the pia-arachnoid. At the base of the left temporal lobe an irregularly shaped excavation due to destruction of the cortex was seen. The area measured 3 by 2.6 by 1 cm in depth and had a grayish-white granular base. The convolutions were flattened. The brain substance was edematous, and the vessels were injected. Frontal sections of the brain showed the ventricles to be normal in size and appearance. An opening was made into the posterior nasal cavity after removal

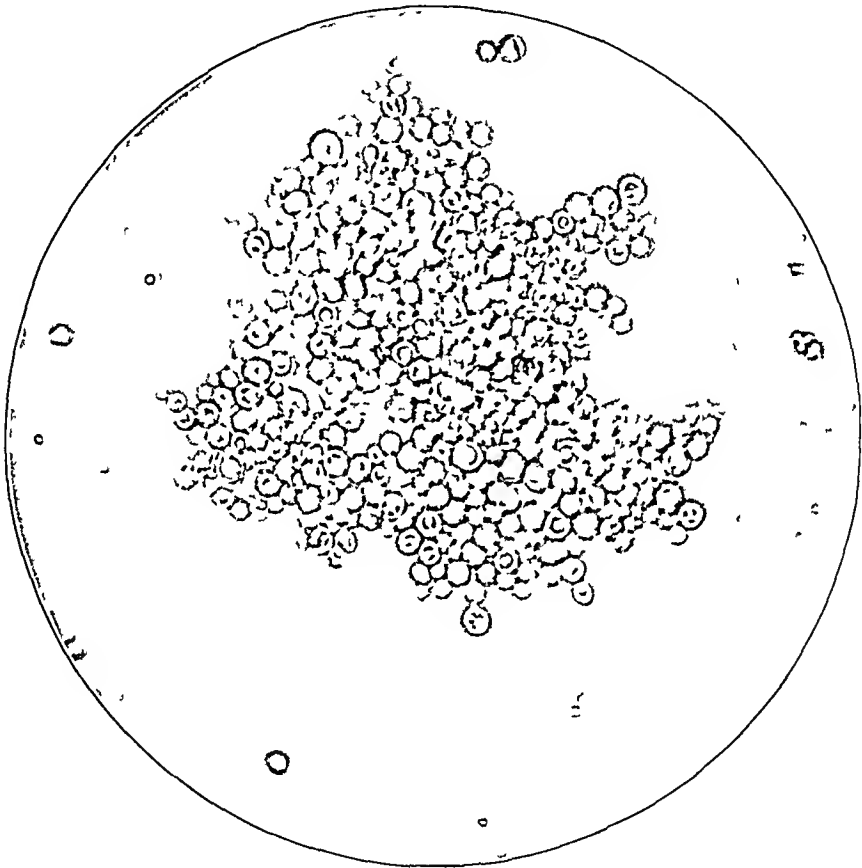


Fig 2—Torula cells, unstained,  $\times 550$

of the sella turcica. The mucous membranes of the sinuses were slightly thickened and injected, and a sphenoid polyposis was present.

The left lung showed edema of the upper lobe and hypostasis of the lower lobe. The pleural cavity contained no fluid. The right pleural cavity contained no fluid. The right lung showed an area of consolidation involving about one third of the upper lobe. The visceral pleura over the lung was smooth, except for a few small adhesive bands at the apex. On section, the consolidated portion was firm in consistency and of grayish-white granular appearance. The consolidated portion resembled a tumor because of its circumscribed and well defined outline. Smears from the cut section of this area of consolidation showed numerous gram-positive yeastlike organisms, some of which were budding. The lower lobe of the right lung showed marked passive congestion with early hypostatic pneumonia.

The pericardial sac contained the normal amount of fluid. The heart was normal in size. On the anterior surface of the right ventricle was an irregular white scar which measured about 2 cm in diameter. The walls of the right ventricle were thin and dilated, while the musculature of the left ventricle showed moderate brown atrophy. The left and right coronary arteries were moderately sclerosed but patent. The heart valves were normal except the mitral valve which was thickened, deformed and scarred. The thoracic aorta showed moderate arteriosclerotic thickening. The abdominal aorta and common iliac arteries showed marked sclerosis.

The liver was normal in size and showed chronic passive congestion. The gallbladder contained one calculus which measured 2 cm in diameter. The walls were thickened, the mucosa was of the cholesteratosis type, and the ducts were patent. The pancreas was soft and apparently normal. The spleen was normal in size, the capsule was thickened, and on section the pulp was soft and

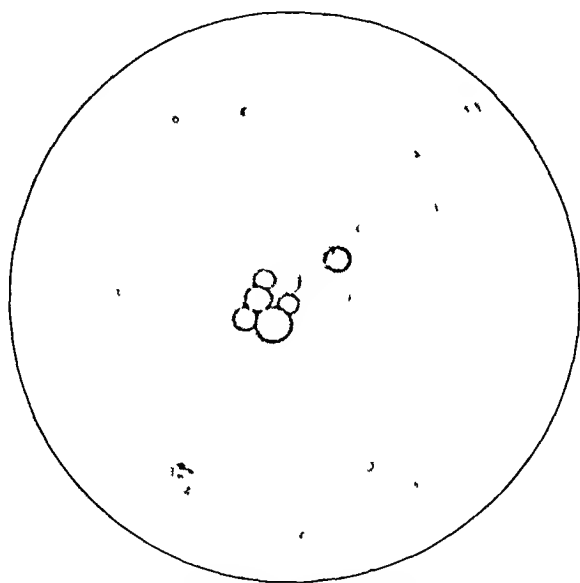


Fig 3—Budding torula cells,  $\times 550$

hemorrhagic. The large and small intestines were normal. The appendix was contracted and of the obliterative type. The left kidney was one-third larger than normal, and fetal lobulations were present. One congenital uriniferous cyst, which measured 5 cm in diameter, was found. The capsule stripped readily, leaving a granular surface. The cortex and medulla were not well differentiated, and the cut surface had a granular appearance. The right kidney was enlarged and essentially the same as the left. The bladder, prostate gland, ureters and urethra were normal.

The mediastinal, peritoneal, retroperitoneal and omental glands were normal.

*Anatomic Summary*—The anatomic examination revealed (1) generalized leptomeningitis and pachymeningitis due to *Torula*, (2) encephalitis with cortical abscess of the left temporal lobe due to *Torula*, (3) sphenoid sinus polyposis, (4) pneumonic consolidation of the apex of the right lung due to *Torula*, passive congestion and hypostatic pneumonia of the left and right lower lobes, (5) chronic myocarditis with dilatation of the right ventricle and chronic mitral endo-

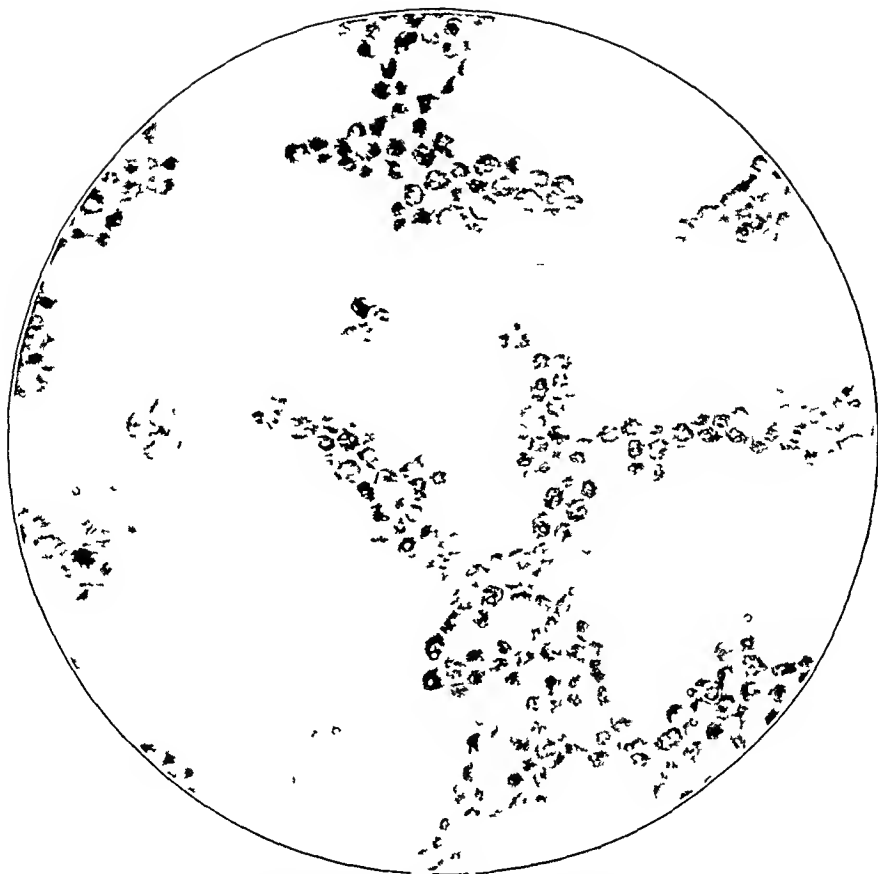


Fig 4—Torula cells stained with methylene blue,  $\times 550$

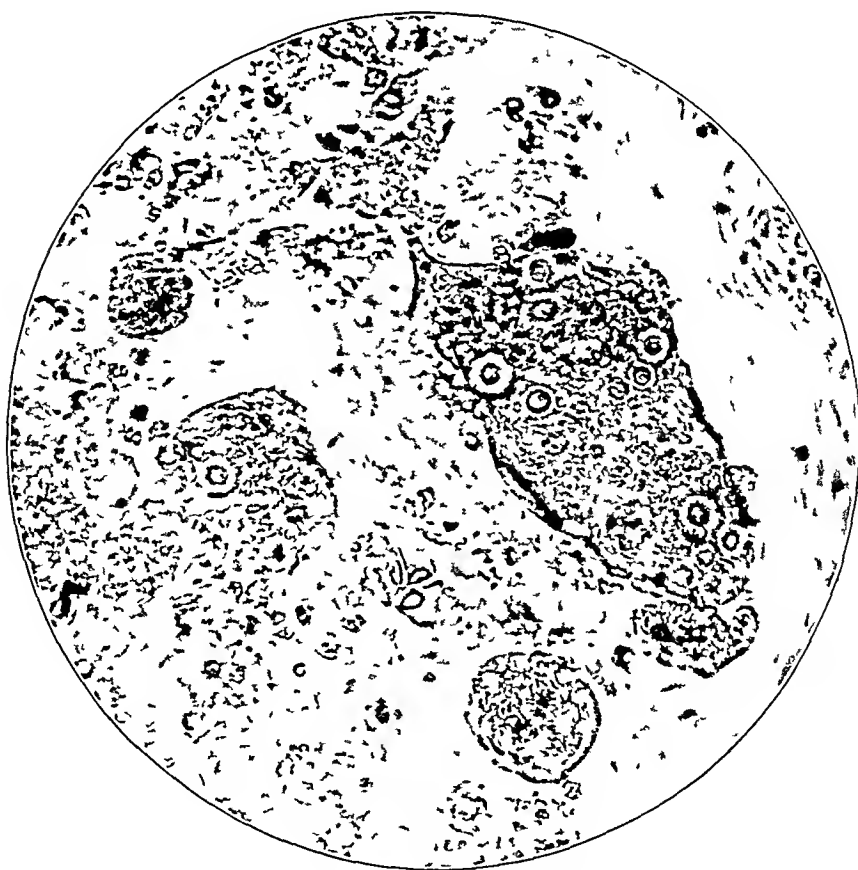


Fig 5—Smear from exudate from the apex of the right lung (unstained),  $\times 200$

carditis, (6) arteriosclerosis, especially marked in the abdominal aorta and common iliac arteries, (7) chronic passive congestion of the liver, (8) chronic cholecystitis and cholelithiasis, (9) chronic splenitis with passive congestion, (10) fetal lobulations and congenital uriniferous cyst of the left kidney, and (11) chronic diffuse nephritis of arteriosclerotic type, with cloudy swelling

*Histologic Examination*—Sections from the area of consolidation at the apex of the right lung showed marked fibrosis with thickened alveolar walls and areas of infiltration made up largely of mononuclear lymphocytes, plasma cells and giant cells. The alveoli were dilated and contained desquamated epithelial cells and numerous large multinuclear giant cells. Within the giant cells numerous gram-positive yeastlike cells were seen, many of which were surrounded by a clear

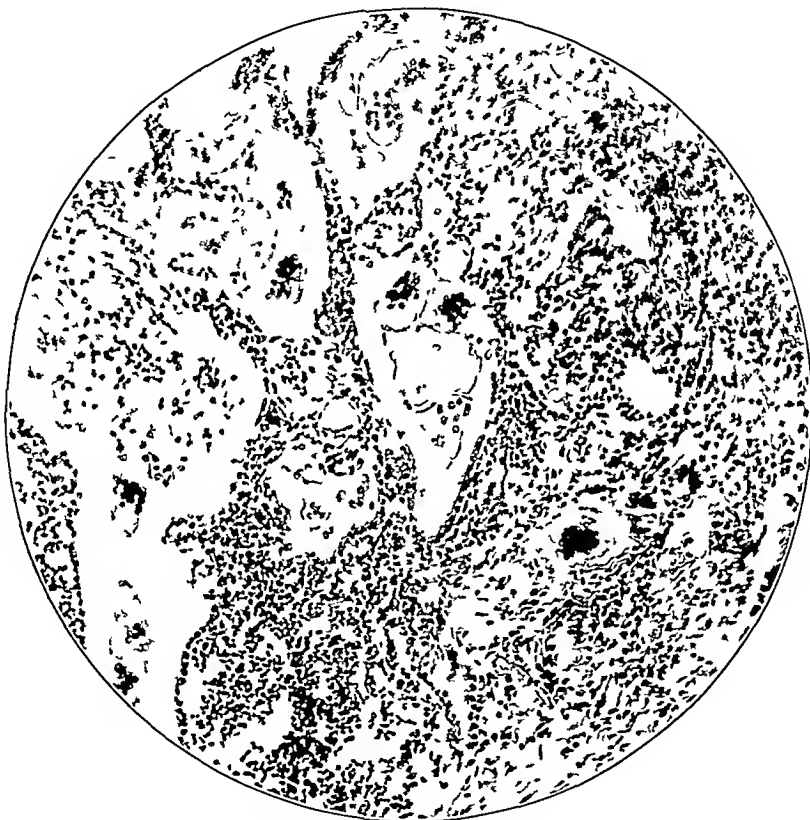


Fig 6—Torula cells in consolidated apex of the right lung,  $\times 100$

capsular-like zone. As many as 9 yeastlike cells could be seen in a single giant cell. Some of the gram-stained sections showed distinct budding of the yeastlike cells. Polymorphonuclear leukocytic infiltration was absent. The walls of the blood vessels were thickened and the lumina of the vessels were engorged with blood cells. There was no evidence of tuberculosis.

Sections from the dura, pia-arachnoid and brain substance showed an inflammatory process without polymorphonuclear leukocytic infiltration. The pia-arachnoid showed a proliferation of the endothelial cells with large multinuclear giant cells containing double-contoured and budding yeastlike cells. A few small areas of necrosis were found. Yeastlike cells were evident in all of the sections. The inflammatory process closely followed the infolding of the pia mater into

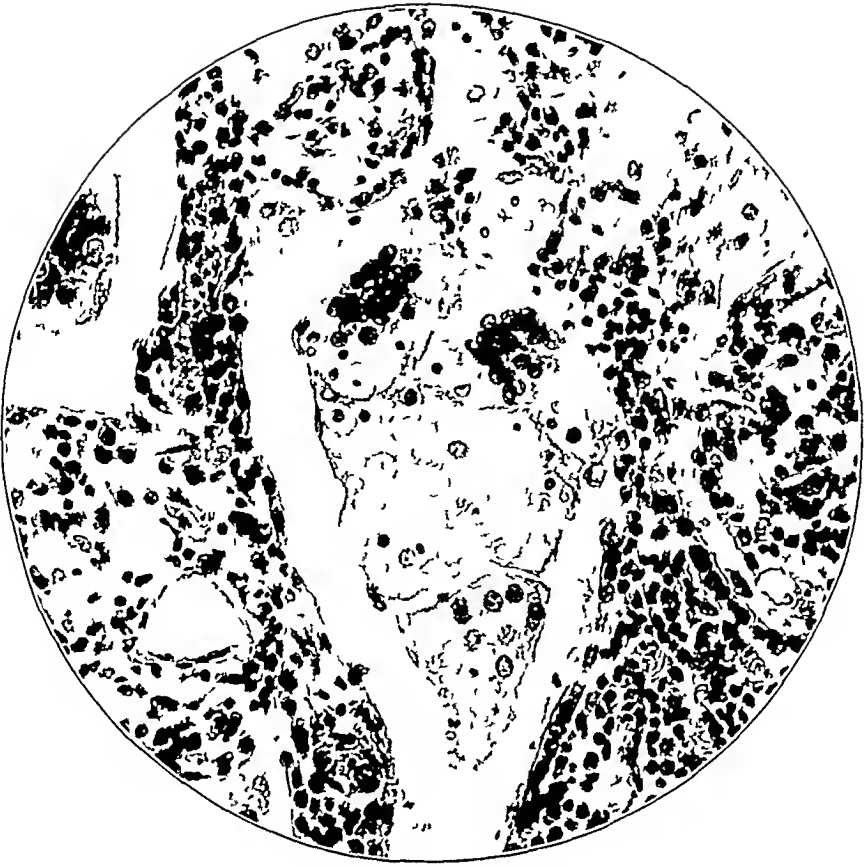


Fig 7—Torula cells in the consolidated apex of the right lung,  $\times 250$

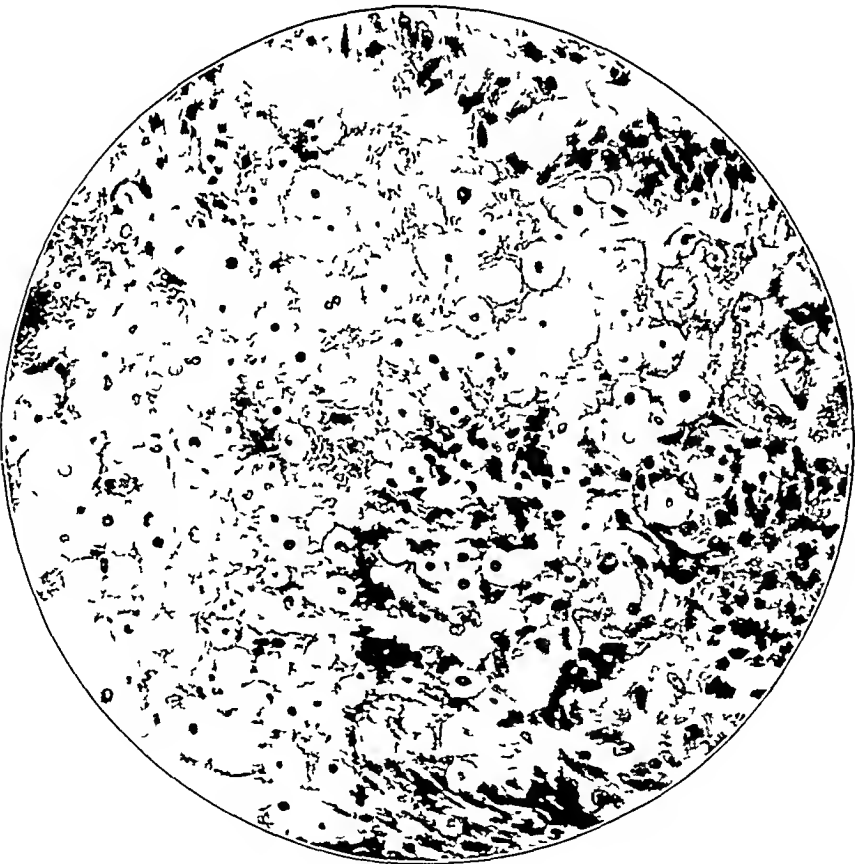


Fig 8—Torula cells in the cortical abscess of the brain,  $\times 250$



the convolutions of the brain. The area of cortical destruction in the left temporal lobe showed marked proliferation of the endothelial cells, large giant cells, plasma and round cells and a great many yeastlike cells, both within and without the giant cells. The yeastlike cells were more numerous in this area than in any of the other sections. As many as twenty-one inclusions were noted in one large giant cell. The subcortical sections from this area showed cells which stained indistinctly, the blood vessels were markedly engorged and the presence of a few giant cells was noted.

The sections of the kidney showed a moderate grade of chronic interstitial nephritis probably dependent on the arteriosclerotic changes. The glomeruli were injected, and the epithelia of the tubules showed marked cloudy swelling.

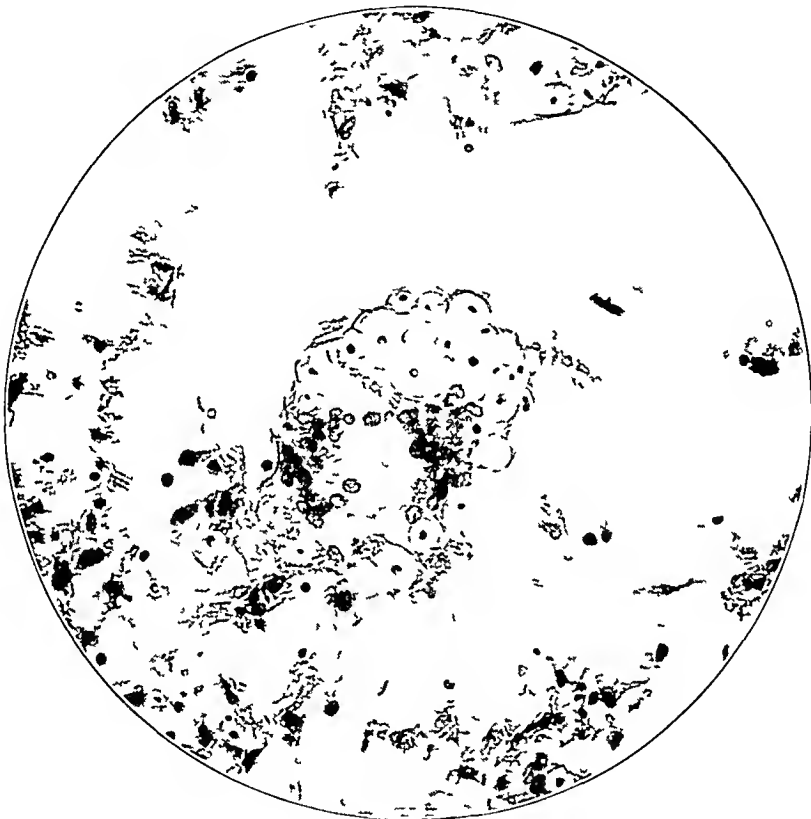


Fig 9—Torula cells in the meningeal exudate,  $\times 250$

The sections of the spleen showed chronic splenitis with marked passive congestion. Those of the liver showed marked passive congestion with moderate fatty infiltration.

*Histologic Summary*—The histologic examination revealed (1) pneumonic consolidation of the apex of the right lung with fibrosis of the alveolar walls and an exudative and infiltrative inflammatory reaction characterized by the presence of numerous giant cells with inclusions of *Torulae* and the absence of polymorphonuclear leukocytes, and (2) meningo-encephalitis with localized abscess formation in the left temporal cortex of the brain. The inflammatory process was characterized by the absence of polymorphonuclear leukocytic infiltration and the presence of many giant cells which contained *Torulae*.

## CONCLUSIONS

1 The primary focus of *Torula* infection at the apex of the right lung may have existed for a long period as a latent infection. There were no clinical symptoms by which the presence of such a focus might be suggested. Hematogenous metastasis to the meninges appeared, probably followed by the relatively slow development of meningeal symptoms. The meningitis and encephalitis during development were characterized by the absence of fever, nausea, rigidity or retraction of the neck and by the absence of the degree of leukocytosis present in other infections of these tissues.

2 The pathologic lesions in torulosis are distinctive and are characterized by the presence of numerous giant cells with inclusions of *Torulæ* and by the absence of polymorphonuclear leukocytes.

3 No form of treatment for torulosis has been found beneficial. *Torula* infection, when it occurs in man, seems to have a predilection for the central nervous system, and all reported cases have resulted in fatal termination.

4 When possible, torulosis should be differentiated from oidiomycosis with systemic invasion by culture studies, since the iodides in large doses have been found of value in the treatment of patients with oidiomycosis.

# DIABETES MELLITUS

## PATHOLOGIC CHANGES IN THE SPINAL CORD AND PERIPHERAL NERVES <sup>1</sup>

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The physician who has much to do with diabetes is soon aware of the significance of the neurologic accompaniments of this disease. In von Noorden's <sup>1</sup> experience, pain occurred in 31 per cent of all cases. In our cases, peripheral pain, which could not be attributed to arthritis, myositis or trauma, has been severe enough to be recorded in about 10 per cent of all cases. As a rule such pains are confined to the legs, especially to the calves. They are usually tolerable, but may become excruciating. They are usually dull, aching and constant, but may simulate the darting pains of tabes. They are as a rule more intense when the patient is quiet and in bed, but may be of the type of claudication, aggravated by exercise.

The complaint of numbness of the feet or legs is as frequent as the complaint of pain in cases of diabetes. Such numbness may occur as a solitary symptom but is usually associated with pain. In a recent period of five years we have seen 33 instances of anesthesia and 92 of paresthesia among approximately 2,000 patients with diabetes. As is true of the pains, this anesthesia and paresthesia is, with rare exception, limited to the legs.

Less common than pain or paresthesia are trophic lesions. A typical mal perforant was seen in ten cases of the series referred to, the lesion usually affecting the ball of the foot. That such a lesion is trophic in the sense that it owes its origin to a primary disturbance of the nervous system is possibly an open question, it may result from a defective blood supply, it rarely, if ever, occurs in other cases than in cases of advanced atherosclerosis.

The skin of the feet and legs of patients with diabetes and atherosclerosis is abnormally sensitive to injury, so that a degree of heat or cold or an exposure to the roentgen rays which would be tolerated perfectly by a healthy man may produce severe and irreparable lesions.

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1 Von Noorden C H. Die Zuckerkrankheit und ihre Behandlung, Berlin, Julius Springer, 1927, p. 627.

Patellar and tendo achillis reflexes are often absent or greatly diminished in diabetes. Borchardt<sup>2</sup> recorded these abnormalities in 37 per cent of all his cases. As Williamson<sup>3</sup> pointed out, the stage of the illness and previous care of the patient influence this percentage to a wide degree.

The skin reflexes, particularly the plantar responses, on the other hand, are rarely abnormal, and motor disturbances are rare. During a period of five years, motor weakness was recorded in only twenty-nine cases, the peroneal group of muscles was affected in most of these.

Occasionally, but rarely, the various neurologic disturbances of diabetes are sufficiently intense and so associated in the same patient as to give a clinical picture that is not dissimilar to that of tabes dorsalis. Various names have been applied under these circumstances, especially polyneuritis diabetica, tabes peripherica diabetica and pseudotabes diabetica. The condition was recognized simultaneously in 1884 by Althaus<sup>4</sup> and Borchardt. Joslin<sup>5</sup> has observed six cases of such polyneuritis, two of the patients were addicted to alcohol. We have seen four cases of this condition, two of which are reported here. Von Noorden has observed three cases, one in a patient addicted to alcohol.

Areflexia and the pain and paresthesia of diabetes occur commonly in patients who are receiving treatment and whose diabetes is thoroughly under control, that is, in patients who are free from either acidosis or glycosuria. It is important to distinguish sharply between the neuritis that arises in such cases and conditions encountered in patients with uncontrolled diabetes. In the era before insulin it was usually possible to prevent glycosuria, in severe cases of diabetes, only by ruthless starvation. This resulted in cachexia. Also, patients whose diabetes was not controlled became cachectic as a result of the wasting effect of the disease. Areflexia was frequently encountered then in juvenile patients who now, with better treatment, almost never present any neurologic complications. This was due in all probability to the cachexia. At least this explanation was suggested in 1922. In that year insulin became available and previously cachectic patients in large numbers were returned to a normal state of nutrition. In many instances (all of the juvenile cases) the reflexes returned with the return of the normal state of nutrition.

2 Borchardt, Harold. Ueber die Veränderungen der Arterienmedia bei Spontangangran und ihre Beziehung zum Diabetes, *Virchows Arch f path Anat* **259** 521, 1926.

3 Williamson, R. T. On the Knee-Jerks in Diabetes Mellitus, *Lancet* **2** 138, 1897, *Diabetic "Neuritis," Practitioner* **112** 85, 1924.

4 Althaus, Julius. On Sclerosis of the Spinal Cord, Including Locomotor Ataxia, Spastic Spinal Paralysis and Other System-Diseases of the Spinal Cord. Their Pathology, Symptoms, Diagnosis and Treatment, London, Longmans, Green & Company, 1885, p. 278.

5 Joslin, E. P. The Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, 1928, p. 998.

This distinction between impairment of reflexes due to cachexia in diabetes and areflexia, such as is observed in the cases we are reporting here, has not been made before. Similarly, a sharp distinction has not been drawn between the types of neuralgia with which we are concerned in this report and the pains that frequently accompany diabetic acidosis. Not only was it usually impossible, in the era before insulin, to prevent glycosuria in severe cases, but it was usually impossible to avoid ketosis. Patients of those days seemed to become habituated to the ketone bodies and would live for months and years with large concentrations of oxybutyric acid in the blood and urine. Diabetic acidosis, as is well known, produces pains. These may be of great intensity, and as they commonly affect the abdomen they may simulate a gastric crisis or a surgical emergency such as appendicitis, or they may be more diffuse and be felt in the back, the neck or the extremities. It is now known that these pains are immediately relieved when the ketosis is checked with insulin. It is improbable, therefore, that such impermanent pains represent lesions of the nerves, although it is possible that long-continued ketosis might give rise to toxic degeneration of the nerves. In any case, such pains undoubtedly have been confused in the past, particularly in cases of chronic ketosis, with the types of neuralgia that occur in milder cases of diabetes, this has introduced confusion into the discussions of diabetic neuritis. In this paper we are not concerned with areflexia from cachexia or with the pains of diabetic acidosis. Our observations are limited to patients who were well nourished and whose diabetes was well controlled.

#### HISTORICAL REVIEW

The recent literature contains practically no reports of the histology of the cord and nerves in diabetes, and the older writers who established the current views of diabetic neuritis left relatively few descriptions that are entirely satisfactory. The reports of observations that many thought indicative of pathologic states would now be considered unwarranted or as reports of conditions falling within the normal range. Certain technical aids in which we now place reliance were not at the disposal of some of the early writers, correlated studies of clinical symptoms and pathologic data were seldom obtained, and until insulin was discovered it was often extremely difficult to distinguish between the symptoms that persist after the disappearance of cachexia and acidosis and those now attributable to cachexia or acidosis.

It is important also to recognize that diabetes frequently has associated with it other disturbances which may produce degeneration of nervous tissues when they occur independently, such conditions are alcoholism, syphilis, tuberculosis, acute infections, senility and atherosclerosis. The presence of any of these in a given case of diabetes with

neuritis immediately raises the question as to whether the complication or the diabetes is responsible for any degeneration noted in the spinal cord or nerves

Brief mention of the causes to which changes found in the cord, roots and peripheral nerves have been attributed includes the following: the deleterious action of sugar, acetone, diacetic acid and unknown intermediate metabolites, dehydration, anoxemia, inanition, arteriosclerosis and complicating infections. Labbé and Gendron,<sup>6</sup> Femblatt<sup>7</sup> and others have reported the presence of ketone bodies in the spinal fluid, but in none of these cases was there a report of necropsy. Kiefer, Brigham and Wheeler<sup>8</sup> found large amounts of sugar in the spinal fluid, but here too there were no reports of necropsy.

A few experimental studies have been made. In 1890, Auché<sup>9</sup> applied a solution of sugar to the sciatic nerves of guinea-pigs, locally and by injection. He said that the action of the sugar was like that of water, and he did not believe that sugar was a cause of degeneration. In 1892, Eichhorst<sup>10</sup> kept nerves of frogs and man in solutions of dextrose, acetone and oxybutyric acid for several days without effect. Grube,<sup>11</sup> in 1918, made reference to some earlier experiments in which he had observed marked neuritis after subcutaneous or intravenous injection of dextrose into rabbits.

Patrick<sup>12</sup> suggested that the neuritis seen in diabetes may be the result of infection to which patients with diabetes were formerly notoriously susceptible. In 1879, Savory and Butlin,<sup>13</sup> speaking of perforat-

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6 Labbe, Marcel, and Gendron, Andre. Diagnostic du coma diabétique, les reactions d'acidose dans le liquide cephalo-rachidien, *Paris med* **13** 181, 1914.

7 Femblatt, H. M. Report of a Fatal Case of Juvenile Diabetic Coma with Insignificant Ketonuria, and with a Large Amount of Acetone in the Spinal Fluid, *Arch Int Med* **34** 508 (Oct.) 1924.

8 Kiefer, E. D., Brigham, F. G., and Wheeler, R. R. Embolic Gangrene of the Extremities in Pneumonia. Report of Case Occurring in Diabetic Coma with an Observation on the Sugar Content of Cerebrospinal Fluid During Insulin Shock, *Boston M & S J* **194** 191, 1926.

9 Auché, B. Des alterations des nerfs peripheriques chez les diabetiques, *Arch d med exper et d'anat path* **2** 635, 1890.

10 Eichhorst, Hermann. Neuritis diabetica und ihre Beziehungen zum fehlenden Patellarschnenreflex, *Arch f path Anat* **127** 1, 1892.

11 Grube, Karl. Ueber das Verhalten der Patellarreflexe bei Diabetes mellitus, *Neurol Centralbl* **12** 770, 1893, Gastrische Krisen bei Diabetes mellitus nebst Bemerkungen uber die Behandlung der Verdauungsstorungen der Diabetiker, *Munchen med Wchnschr* **42** 136, 1895, Ueber das Verhalten des Blutzuckers im Fallen von diabetischer Neuritis und Neuralgie, *Deutsche Ztschr f Nervenhe* **60** 302 1918.

12 Patrick, H. T., in discussion on Krauss, W. M. Involvement of Peripheral Neurons in Diabetes Mellitus, *Arch Neurol & Psychiat* **7** 202 (Feb.) 1922.

13 Savory, W. S. and Butlin, H. T. Cases of Perforating Ulcer of the Foot, *Tr Roy Med & Chir Soc* **62** 373, 1879.

ing ulcers, although neither of their patients had diabetes, believed that degeneration of the nerves, rather than vascular changes, was responsible for the ulcers. Kirrnisson,<sup>14</sup> in 1885, stated it as his belief that the malperforant of diabetes is caused by neuritis.

Arteriosclerosis is a common complication of the diabetes that occurs among middle-aged or older persons, as is generally well known. It is demonstrable in practically all cases with gangrene and is often the cause of death in the diabetes of older patients.

Forty-two cases in which there was a pathologic description were reviewed from the literature. In sixteen cases there was evidence of degeneration of the funiculi of the cord, chiefly in the posterior column, in four cases, degeneration of the intramedullary portion of the posterior roots was specifically mentioned, in eight, there were variable changes in the cells of the anterior horn, and in twenty-four, there was degeneration in the peripheral nerves.

The changes in the spinal cord have been interpreted differently by various authors. Sandmeyer,<sup>15</sup> Leyden and Goldscheider<sup>16</sup> and Naunyn<sup>17</sup> believed that the degeneration noted was of the type known as combined sclerosis, first described by Lichtheim<sup>18</sup> in association with pernicious anemia. Williamson<sup>19</sup> and Schweiger<sup>20</sup> maintained that the changes in the posterior columns were secondary to "pluriradicular" degeneration, that is, to degeneration in the intramedullary portion of the posterior roots. As the degeneration was traced upward in the cord, it approached nearer and nearer the median line. Williamson<sup>21</sup> presented photographs which showed the intramedullary portion of the posterior root in a stage of degeneration, and stated that the degeneration was practically absent

14 Kirrnisson, quoted by Remak, Ernest, and Flatau, Eduard. *Neuritis und Polyneuritis*, in Nothnagel, Herman. *Specielle Pathologie und Therapie*, Vienna, Holder, 1900, vol 11, p 150.

15 Sandmeyer Wilhelm. *Beitrag zur pathologischen Anatomie des Diabetes mellitus*, *Deutsches Arch f klin Med* **50** 381, 1892.

16 Leyden and Goldscheider. *Die Erkrankungen des Rückenmarks und der Medulla oblongata*, in Nothnagel, Herman. *Specielle Pathologie und Therapie*, Vienna, Holder, 1900, vol 10, p 500.

17 Naunyn, Bernard. *Der Diabetes mellitus*, in Nothnagel, Herman. *Specielle Pathologie und Therapie*, Vienna, Holder, 1900, vol 7, p 251.

18 Lichtheim, quoted by Sandmeyer, Wilhelm. *Deutsches Arch f klin Med* **50** 381, 1892.

19 Williamson, R. T. *Changes in the Spinal Cord in Diabetes Mellitus*, *Brit M J* **1** 122, 1904, *The Symptoms Due to Peripheral Neuritis or Spinal Lesions in Diabetes Mellitus*, *Rev Neurol & Psychiat* **5** 550, 1907, *Diseases of the Spinal Cord*, London, Frowde, Hodder and Stoughton, 1908, p 371, footnote 3, second reference.

20 Schweiger, L. *Ueber die tabiformen Veränderungen der Hinterstränge bei Diabetes*, *Wien med Wchnschr* **57** 1549, 1907.

21 Williamson (footnote 19, first and third references).

external to the pia mater. In the opinion of Williamson<sup>22</sup> and Schweiger, the changes were like those seen in tabes, except, Schweiger added, that the roots were less completely involved, owing to the shorter duration of the diabetic changes. Kraus,<sup>23</sup> in his study, concluded that clinical evidence favors the assumption that both motor and sensory phenomena are best explained by a lesion proximal to the junction of the roots, and that Buzzard's<sup>24</sup> case alone suggested true peripheral sensorimotor neuritis. The evidence for this is not convincing.

Degeneration in the cells of the anterior horn, noted in eight cases, was slight, except in the two cases reported by Nonne<sup>25</sup> and Bonardi.<sup>26</sup> It may justly be questioned whether these changes were a consequence of diabetes.

Degeneration of the peripheral nerves has been the most frequent observation. Charcot,<sup>27</sup> in a delightfully written contribution, insisted that peripheral neuritis must be the cause of most diabetic disorders falling in this class. He described the gait as "démarche de steppe," and insisted that true ataxia, as seen in these patients, exists only when true tabes is complicated with diabetes mellitus.

#### CASES REPORTED IN THE LITERATURE

Rosenstein<sup>28</sup> (1885)—In a man, aged 34, with absent patellar reflexes, there were no changes in the spinal cord. Tuberculosis was present.

Pryce<sup>29</sup> (1887)—A man, aged 56, a sufferer from alcoholism, had polyuria of eighteen months' duration, he had ulcers of both feet, and complained that his feet felt dead. The pupillary reaction to light was feeble, the patellar reflexes were absent, and sensation in the lower third of the legs was reduced. At necropsy, the posterior right tibial nerve was found embedded with an atheromatous artery in scar tissue. The cells in the spinal cord, particularly in the thoracic region, were atrophic, granular and without normal processes. In the right posterior

22 Williamson (footnote 19, third reference)

23 Kraus, W. M. The Clinical Involvement of the Peripheral Nerves in Diabetes Mellitus, *J Nerv & Ment Dis* **52** 331, 1920, Involvement of the Peripheral Neurons in Diabetes, *Arch Neurol & Psychiat* **7** 202 (Feb.) 1922.

24 Buzzard, Thomas. A Case of Symmetrical Sciatica in a Diabetic Patient Treated by Salicylate of Soda, *Lancet* **1** 302, 1882.

25 Nonne, M. Ueber Poliomyelitis anterior chronica als Ursache einer chronisch progressiven atrophischen Lahmung bei Diabetes mellitus, *Berl klin Wchnschr* **33** 207, 1896.

26 Bonardi, Edoardo. Sclerosi diffusa pseudo-sistematizzata della midolla spinale con polinevrite in un caso di diabete mellito, *Morgagni* **39** 557, 1897.

27 Charcot, J. M. Sur un cas de paraplegie diabétique, *Arch de neurol* **19** 305, 1890.

28 Rosenstein, S. Ueber das Verhalten des Kniephänomens beim Diabetes mellitus, *Berl klin Wchnschr* **22** 113, 1885.

29 Pryce, T. D. A Case of Perforating Ulcers of Both Feet Associated with Diabetes and Ataxic Symptoms. *Lancet* **2** 11, 1887.



tibial nerve, and to a less extent in the anterior tibial nerve, a granular myelin sheath was found which did not stain black with osmic acid. Many degenerated axis cylinders were noted.

*Nonne* (1889) — CASE 1 — A man, aged 27, had alcoholic epilepsy and possibly healed tuberculosis. Patellar reflexes were absent. At necropsy, the spinal cord was found to be normal. There was parenchymatous degeneration of the nerves to the vastus internus, rectus femoris and sartorius muscles.

CASE 2 — In a man, aged 44, the patellar reflexes were absent. At necropsy, the spinal cord was found to be normal. The peripheral nerves showed changes similar to those described in the preceding case.

CASE 3 — In a man, aged 55, an alcoholic patient, patellar reflexes were absent. Hepatitis was present. At necropsy, similar changes in the cord and the peripheral nerves were present.

CASE 4 — A man, aged 49, had pulmonary and intestinal tuberculosis. At necropsy, abnormalities in peripheral nerves similar to those in the preceding cases were found. There was slight degeneration of the muscles. The spinal cord was normal.

CASE 5 — A man, aged 46, died from typhoid fever. At necropsy, he was found to have a normal cord and changes in the peripheral nerves as described in case 4.

*Auche*<sup>9</sup> (1890) — CASE 1 — A patient, aged 74, had gangrene of the right foot and muscular cramps, the right femoral artery was thrombosed. Pulsation of the popliteal and pedal arteries was absent. At necropsy, the spinal cord was found to be normal macroscopically and the nerves in the right leg were fragmented.

CASE 2 — The patient, aged 50, had had glycosuria for six years, weakness of the lower extremities and a prickling sensation in the legs, feet and hands. The patellar reflexes were absent. At necropsy, the spinal cord was normal to macroscopic examination. The posterior tibial nerve contained segmented, irregular, shrivelled and poorly stained sheaths. The plantar nerves were markedly degenerated, and branches of the radial nerve were degenerated.

CASE 3 — The patient, aged 19, had had diabetes for three months, cramps in the calves of the legs, slight analgesia over the dorsum of the forearms and hemorrhages under the nails of the toes. The patellar reflexes were absent. At necropsy, the spinal cord appeared normal on macroscopic examination. There was parenchymatous neuritis of the nerves of the fingers and lower extremities.

*Eichhorst*<sup>10</sup> (1892) — CASE 1 — A patient, with normal sensation, without any tendon reflexes of the lower extremities but with ankle clonus (?), died in coma. At necropsy, examination of the spinal cord was negative, and there was degeneration of the sciatic, crural and vagus nerves.

CASE 2 — A patient without patellar reflexes died in coma. At necropsy, the spinal cord was found to be normal, and there was degeneration of the sciatic and crural nerves.

In both of Eichhorst's cases, the crural nerves were markedly degenerated, and there was cellular infiltration.

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30 Nonne, M. Einige anatomische Befunde beim Mangel des Patellar-Reflexes, Festschr. z. Eröffn. d. u. allg. Krankenh. zu Hamb.-Eppendorf, 1889, p. 144.

*Sandmeyer*<sup>30</sup> (1892) —A girl, aged 9 years, had had diabetes for two years. The reflexes were normal. She died in coma. At necropsy, there was degeneration near the posterior median septum in the cervical and thoracic regions.

*Pryce*<sup>31</sup> (1893) —CASE 1 —A man, aged 72, had bilateral sciatica. A sensation of burning and lightning pains of the lower extremities had been present for fourteen years. There was gangrene of the left foot and leg, sensation was slightly decreased over the feet, and patellar reflexes were absent. At necropsy, the posterior tibial and sciatic nerves showed a granular myelin sheath, degeneration of many axis cylinders and poor staining qualities. Atheroma of the blood vessels was present.

CASE 2 —The patient, who had had diabetes and gangrene of the right foot for six years, complained of shooting and burning pains in both legs and of tenderness of the feet. Sensation in the feet was diminished, and edema was present. The patellar reflexes were absent. At necropsy, parenchymatous changes were found in the nerves and atheroma in the blood vessels, as in the preceding case.

*Cavazzani*<sup>32</sup> (1893) —A woman, aged 20, was studied chiefly from the standpoint of the visceral nervous system. At necropsy, the spinal cord was normal.

*Leichtentritt*<sup>33</sup> (1893) —A woman, aged 60, had had diabetes for six years. She suffered from vertigo, tearing pains in the entire body, left hemiplegia, defective memory and indistinctness in speech. Sensibilities to pain and temperature were absent over the left foot, tactile sensation was normal. Sensibility to pain was diminished over the outer surface of the right leg. The left popliteal artery was thrombosed. There was old and recent mitral disease. At necropsy, the spinal cord showed some degeneration in the posterior columns, some increase in connective tissue, corpora amylacea, thickened pia mater and granular, yellow cells of the anterior horn with thick, short processes. There was some degeneration of the nerves of the lower extremities. The vagus was normal.

*Leyden*<sup>34</sup> (1893) —The patient suffered from weakness and tenderness of the legs, nephritis and arteriosclerosis. The patellar reflexes were absent. At necropsy, degeneration was found in the posterior and lateral columns of the spinal cord and of the tibial nerve.

*Williamson*<sup>35</sup> (1894) —CASE 1 —A patient, aged 52, had had diabetes for eleven months. There were numbness and tingling of the fingers, marked atherosclerosis and wasting of the deltoid triceps and biceps muscles. At first the patellar reflexes were absent, they later returned. At necropsy, pulmonary tuberculosis was disclosed. There was calcification of the vessels, some degeneration of the posterior columns of the cord in the cervical and thoracic regions and an increase in the number of neuroglia. Nerves to the biceps muscles were normal.

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31 Pryce, T. D. On Diabetic Neuritis with a Clinical Pathologic Description of Three Cases of Diabetic Pseudotabes. *Brain* 16 416 1893.

32 Cavazzani, A. Sympathicusveränderungen bei Diabetes mellitus, anatomische und mikroskopische Beiträge, *Zentralbl. f. allg. Pathol. u. path. Anat.* 4 501, 1893.

33 Leichtentritt, Heinrich. Ein Beitrag zur Erkrankung peripherer Nerven und des Rückenmarks bei Diabetes mellitus, Berlin, G. Schade, 1893 p. 32.

34 Leyden. Bemerkungen über Diabetes mellitus, *Deutsche Med.-Ztg.* 44 497 and 507 1893.

35 Williamson, R. T. Changes in the Posterior Columns of the Spinal Cord in Diabetes Mellitus. *Brit. M. J.* 1 398, 1894.

CASE 2—A woman, aged 21, had had diabetes for one and a half years, with pains in the feet and ankles and advanced pulmonary tuberculosis. The patellar reflexes were absent. At necropsy, the spinal cord showed changes similar to those noted in case 1, but less marked, the crural nerves were normal.

The spinal cords of three other patients were studied and found to be normal.

*Nonne*<sup>22</sup> (1896)—A patient aged 64, had had diabetes for four years. There were progressive weakness of the upper and lower extremities, dysphagia, dysarthria and atrophy of the Aran-Duchenne type. The patellar reflexes were absent. Pulmonary complications developed. At necropsy, marked degeneration of the cells of the anterior horns was found. The posterior roots were normal, there was diffuse rarefaction of the spinal cord "like in pernicious anemia." The median and tibial nerves were about a third degenerated.

*Fraser and Bruce*<sup>36</sup> (1896)—A man, aged 36, had had diabetes for fourteen months. He complained of feebleness, amblyopia and cramps in the calves and ankles. His legs were tender, the patellar reflexes were absent, and the fundi of the eyes were without abnormality. At necropsy, pulmonary tuberculosis, parenchymatous degeneration and increase in the connective tissue of the optic nerves were found. Also, there was marked degeneration of the tibial nerves. The muscles showed fine granules between the fibers and loss of transverse striations, a condition which is referred to as "disseminated interfibrillary fatty degeneration," and which differs from that seen following section of the nerves.

*Kalmus*<sup>3</sup> (1896)—CASE 1—A man aged 26, had syphilis and suffered from vomiting and diarrhea. The patellar reflexes were absent. At necropsy, gastroenteritis and nephritis were found. The posterior columns of the spinal cord were markedly degenerated, more on the right than on the left side. The pia mater was slightly thickened. The central canal was filled with lymphoid cells.

CASE 2—A man, aged 30, had pulmonary tuberculosis. Sensation and reflexes were normal. At necropsy, marked tuberculosis was discovered. Degeneration of moderate intensity of the posterior columns also was present.

*Souques and Marinesco*<sup>38</sup> (1897)—The history was not given. Necropsy disclosed degeneration of the posterior columns.

*Bonaldi*<sup>37</sup> (1897)—A patient, aged 72, complained of thoracic pain, formication and a feeling of deadness in the arms. There were mild thoracic kyphosis, decubitus, feebleness and wasting of the upper extremities, slight numbness of the feet and hands, atrophy of the calves of the legs and marked impairment of the patellar reflexes. The patient had a spastic, parietic gait, and presented the clinical picture of bulbar paralysis with loss of sphincteric control. At necropsy, profuse arteriosclerosis and pulmonary tuberculosis were found. The pia mater was thickened and adherent to the cord in the cervical region, the cells of the anterior horn were diminished in volume and stained poorly, and the bulbar nuclei were atrophic. The nerves of the upper and lower extremities showed interstitial and parenchymatous neuritis with an increased amount of connective tissue and an increased number of nuclei. The vagi were normal. The muscles had lost their striations, and their nuclei were increased in number.

36 Fraser, T. R., and Bruce, A. On a Case of Diabetic Neuritis, with a Description of the Post-Mortem Examination of the Nerves and Muscles, *Edinburgh M. J.* 42 300, 1896.

37 Kalmus, Ernst. Beitrag zur Kenntniss der Rückenmarkserkrankungen bei Diabetes mellitus, *Ztschr. f. klin. Med.* 30 559, 1896.

38 Souques, A., and Marinesco, G. Lesions de la moelle epiniere dans un cas de diabete sucre, *Rev. neurol.* 5 242 1897.

*Hensav*<sup>39</sup> (1897) —CASE 1—A woman, aged 45, had had diabetes for seven months. At necropsy, capillary hemorrhages in the fourth ventricle and irregular degeneration of about half of the fibers of the spinal accessory nerve were found.

CASE 2—A man, aged 36, had had diabetes for fifteen months. He also had pulmonary tuberculosis. At necropsy, the dura in the sacral region was found to be thick. There was a light streak in each posterior column in fixed material but this was not seen in stained sections. The posterior roots in the lumbar area had a clear periphery but swollen myelin sheaths in the center.

CASE 3—A man, aged 68, a sufferer from alcoholism, had had diabetes for eight years. He also had an enlarged liver and spleen, slight ascites and arteriosclerosis. At necropsy, a fresh hemorrhage was found in the fourth ventricle. Both seventh cranial nerves showed a clear periphery and swollen myelin sheaths in the center, as noted in the previous case. Hensav did not know whether this change was an artefact or not.

*Findlay*<sup>40</sup> (1902) —A man, aged 41, had had diabetes for nine months, with shooting pains in the legs. He also had pulmonary tuberculosis. The patellar reflexes were absent. At necropsy, fatty degeneration of the liver and cloudy swelling of the kidneys were found. There was slight sclerosis and infiltration of the pancreas with small round cells. Degeneration and chromatolysis of the cells of the anterior horn and increase in the number of glia cells were found in the spinal cord. There was slight degeneration of the tenth cranial nerve, marked degeneration of the cervical sympathetic nerves and almost complete degeneration of the crural nerve. The rectus abdominis muscle showed few striations, longitudinal splitting and increase in the number of nuclei. Findlay suggested that the neuritis of the tenth cranial nerve may have contributed to the development of both diabetes and tuberculosis.

*Naunyn*<sup>41</sup> (1900) —In a man, aged 41, a stone was found at necropsy in the duct of Wirsung. The spinal cord was normal.

*Ossokine*<sup>42</sup> (1902) —A man, aged 51, died from pneumonia. At necropsy, there were scattered areas of degeneration in the posterior and anterior columns of the spinal cord and some degeneration of cells. In the crural nerves, stained by the method of Marchi, numerous black points were seen.

*Marinesco*<sup>43</sup> (1903) —A man, aged 21, had had diabetes for seventeen months. The lower extremities were extremely weak, the patellar reflexes were absent. At necropsy, the cells of the anterior horn showed perinuclear chromatolysis and displaced nuclei, possibly the result of injury of the peripheral nerves. In the sciatic nerve some degeneration was found, and in the external popliteal nerve there was marked degeneration. The crural nerves were normal.

*Williamson*<sup>43</sup> (1904) —A man, aged 25, had had diabetes for nine months. He also had early pulmonary tuberculosis, and the patellar reflexes were absent. At necropsy, the spinal cord showed a few swollen axis cylinders and an increase

39 Hensav, Joseph. Untersuchungen des Central-Nervensystems bei Diabetes mellitus, Strassburg, Goeller, 1897, p. 38.

40 Findlay, J. W. Changes in the Peripheral Nerves in a Case of Diabetes Mellitus, Tr. Medico-Chir. Soc. Glasgow 3: 441, 1902.

41 Ossokine, N. Contribution a l'etude de l'anatomie pathologique de la moelle dans le diabete sucre, abstr. Rev. neurol. 10: 993, 1902.

42 Marinesco, G. Ein Fall von diabetischer Paraplegie, Neurol. Centralbl. 22: 94, 1903.

43 Williamson (footnote 19, first reference).

in the number of glial cells of the column of Goll, also, there was degeneration of the intramedullary fibers of the posterior roots. This intramedullary degeneration was considered by Williamson to be the origin of ascending degeneration noted in the posterior columns.

*Bramwell*<sup>44</sup> (1907) —A man, aged 56, had had diabetes for eighteen months. He complained of pain in the legs and that his feet felt dead. There were ulcers over the metatarsophalangeal joints, the pupillary reaction to light was feeble. He had arteriosclerosis. Sensation was diminished over the lower third of the legs. Patellar reflexes were absent. At necropsy, the arteries, especially those in the posterior column of the spinal cord, were found to be diseased, and corpora amylacea were present. Most of the fibers were normal. There was some atrophy of the cells of the anterior horn and slight degeneration of the sciatic nerve. The blood vessels generally were sclerotic. There was advanced arteriosclerosis of the posterior tibial artery which was adherent to the posterior tibial nerve. This nerve and the plantar nerve were much degenerated. Bramwell believed that the changes in the nerve were secondary to the scar tissue.

*Schweiger*<sup>45</sup> (1908) —CASE 1 —A man, aged 63, had had syphilis thirty-two years before examination. For two years he had had diabetes. He was suffering from gangrene of the right great toe. At necropsy, arteriosclerosis, obliteration of the pericardial cavity and pleuritis were found. The posterior column of the cord was lighter than the other columns. At higher levels Goll's tract particularly was involved. The intramedullary portion of the posterior roots was rarefied. The glia cells were increased in number.

CASE 2 —A woman, aged 59, had had diabetes for two years. She suffered from headache, failure of vision and tearing pains in the feet. Sensation was diminished over the feet. The patellar reflexes were normal. At necropsy, changes found in the spinal cord resembled those described in the preceding case.

CASE 3 —A preparation of the spinal cord from another case of diabetes showed changes similar to those noted in the preceding two cases.

CASE 4 —Examination disclosed fixation of the pupil on the left, lack of rotation of the globe upward and downward, pulmonary tuberculosis and absence of the left patellar reflex. At necropsy, the spinal cord was normal. This patient gave a history of syphilitic infection twenty years previously.

Schweiger believed that the changes noted in the posterior columns of the spinal cord occur secondary to the involvement of posterior roots, that they resemble the changes of tabes, but that they are less extensive because of the shorter duration of the illness.

#### REPORT OF MAYO CLINIC CASES

Our observations have been made in ten cases. In three of these sections were obtained from the following regions: cervical, upper thoracic, lumbar and sacral regions of the spinal cord, sciatic, femoral, peroneal and tibial nerves, and dorsal intermedial cutaneous, medial plan-

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44 Bramwell, B. Diabetes. Perforating Ulcer of the Foot, Advanced Atheroma of the Posterior Tibial Artery, the Artery Being Adherent to the Posterior Tibial Nerve, Marked Changes in the Posterior Tibial and Plantar Nerves, *Clin Stud* 5 279, 1907.

45 Schweiger, L. Ueber die tabiformen Veränderungen der Hinterstränge bei Diabetes, *Archiv f. d. neurol. Inst. a. d. Wien Univ* 14 391, 1908.

tal and digital nerves of the feet In one case which came to necropsy the spinal cord was not removed, but peripheral nerves were obtained In the remaining six cases, a leg was amputated for gangrene, and the anatomic examination was limited to the nerves of the amputated extremity A few frozen sections were made, but for the most part the tissue was embedded in paraffin and celloidin The stains used were various modifications of Weigert's stain, hematoxylin and eosin, iron hematoxylin, acid fuchsin-amine blue-orange G, Weigert's elastic tissue stain, thionine and the stains of Marchi, of Orlandi together with schallach 1, and of van Gieson

CASE 1—A farmer, aged 55, first consulted the Mayo Clinic on Feb 18, 1925, with the complaint of diabetes Polyuria had occurred when he was 40, but had not persisted More marked polyuria and polydipsia had occurred again when he was 49, and sugar had then been found in the urine Imperfect treatment had been applied for the following six years The urine rarely had been sugar free, except for a short period of starvation at the beginning of treatment The family history was without significant features The patient's previous illnesses included an attack of acute nephritis in childhood, an attack of sciatica on the right side at the age of 35 and influenza with pneumonia at the age of 45 There was no history of venereal infection Tobacco and alcohol had been indulged in moderately The maximal body weight, 212 pounds (96 Kg), had been reached at the age of 45 Since that time a loss of 73 pounds (33.1 Kg) had occurred gradually Other symptoms included progressive loss of strength, dyspnea on exertion, epigastric pain associated with a feeling of fulness and belching after meals Pains and numbness of the legs had begun one year before examination, starting in the toes, gradually increasing in severity and extent, and finally involving both legs from the hips down The pains, which often were sharp and darting, usually more severe between 5 and 9 a m, were relieved rather than exacerbated by exercise, and were aggravated by changes in the weather The numbness affected the feet The inner sides of the thighs and knees were hypersensitive, and the skin of the upper part of the abdomen recently had felt raw, distention pain

The height was 5 feet and 7 inches (170.2 cm) Marked thickening of the palpable arteries was noted, the blood pressure was moderately elevated, being 150 systolic and 90 diastolic, measured in millimeters of mercury Mild diabetic retinitis of the central punctate type was present Severe pyorrhea was noted and also calcified pleuritis over the left lung, the heart was displaced to the left, and there was inversion of the T wave in lead I of the electrocardiogram The liver was enlarged, its lower margin was palpable 3 cm below the costal margin and it was harder than normal The prostate gland was enlarged and boggy The Wassermann test of the blood was performed seven times with negative results Data obtained by spinal puncture were negative except for a positive Nonne test The basal metabolic rate was normal on several trials On the patient's admission, the urine contained 4.2 per cent of sugar but did not contain acetone bodies The blood sugar was 280 mg in each hundred cubic centimeters The reflexes of the left upper extremity were definitely diminished as compared with those of the right upper extremity The patellar reflexes were obtained only on reinforcement The reflexes of the tendo achillis were absent The pupillary reflexes were normal The calves of the legs were tender to pressure but with this excep-

tion muscular tenderness was not present. The superficial sensibility for touch, pain and temperature was slightly decreased over the feet, and sensibility to pain, tested by pricking with a pin, was slightly delayed as compared with tactile sensibility over the feet and back. Vibratory sensibility was slightly reduced over the malleoli.



Fig 1 (case 1) —Sciatic nerve. Circumscribed areas of degeneration, *da*, may be seen among nerve fibers otherwise normal, *nf*, in appearance. A number of sclerotic vessels, *bv*, also are present. Acid fuchsin-aniline blue-orange G stain,  $\times 60$ .

Under management with a suitable diet, and relatively small doses of insulin, glycosuria and hyperglycemia were promptly controlled. Nevertheless, the pains

continued, until some time later some relief was obtained following resort to an exclusive milk diet elsewhere. The relief was transitory. At another time, some benefit apparently was obtained by daily doses of theobromine. In March, 1926, the patient contracted erysipelas of the face, from which he died.



Fig 2 (case 1) —Sciatic nerve. The contrast between normal, *nf*, and degenerated areas, *da* is well marked. Acid fuchsin-aniline blue-orange G stain,  $\times 130$ .

Necropsy disclosed erysipelas of the face, head and neck, with involvement of the superior mediastinum, bilateral bronchopneumonia, old tuberculosis of the left lung with cavitation, obliteration of the pleural cavity with calcification, old



empyema, spina bifida occulta, marked general arteriosclerosis and hyperplastic cirrhosis of the liver, which weighed 2,400 Gm

The examination of the spinal cord and nerve roots showed nothing that might be regarded as abnormal, considering the age of the patient. The walls of the vessels, however, were noticeably thickened. Examination of the peripheral nerves showed rather marked degeneration and arteriosclerosis and a moderate increase in thickness of the perineurium. In the femoral nerve, in which the degeneration was least marked, slight infiltration of small round cells and wandering tissue cells was noted. Scattered nerve bundles of the sciatic nerves were obviously necrosed (figs 1 and 2). In the femoral nerves there was degeneration and arteriosclerosis (fig 3). The marked arteriosclerosis would make one suspect the possibility of some relationship between this and the degeneration of the nerves.

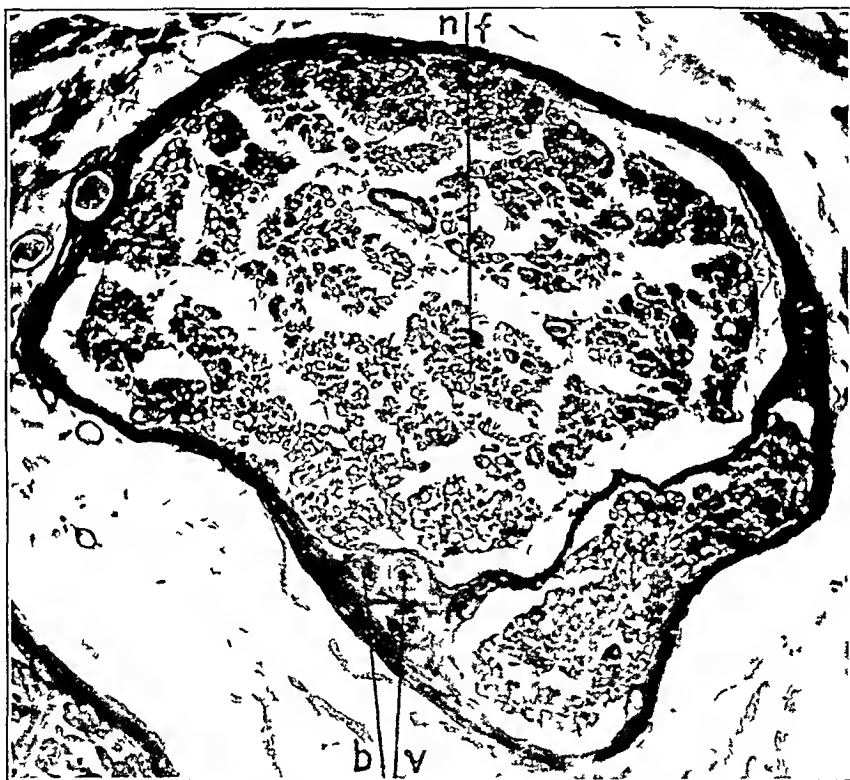


Fig 3 (case 1) —Femoral nerve. Numerous nerve fibers, *nf*, are to be seen, however, many are degenerated, and vessels, *bv*, with thickened walls are in evidence. Acid fuchsin-aniline blue-orange G stain,  $\times 150$

CASE 2 —A farmer, aged 49, first consulted the Mayo Clinic on Dec 22, 1922, with the complaint of ulcers of the toes. Polyuria and polydipsia had been present for four years, during this time a gradual loss of strength had occurred and the weight had fallen from 240 to 178 pounds (108.8 to 80.7 Kg). The urine had been examined shortly before admission and sugar had been found. For a year, the feet had been numb and cold, and blisters of the toes leading to discoloration and ulcers had occurred on Nov 1, 1922. Four other members of the family had had diabetes: the father, a sister and two brothers. The patient did not have children. The previous illnesses included gonorrheal infection at the age of 27 and pneumonia at the age of 42. There was no history of syphilis. He had used tobacco and alcohol moderately for years.

Examination revealed a sturdy man 6 feet (183 cm) in height, weighing 178 pounds, with gangrenous ulcers of both great toes. Other significant observations were the following: blood pressure 112 systolic and 78 diastolic, in the eyegrounds, some irregularity of arterial reflexes but absence of definite arteriosclerosis, one questionable, small, punctate retinal hemorrhage, and absence of reflexes in both the patella and the tendo achillis. The first twenty-four hour specimen of urine after admission to the hospital contained 271.3 Gm of sugar, but acetone was not present, the blood sugar after fasting was 250 mg in each hundred cubic centimeters. The Wassermann reaction of the blood was negative. After several weeks spent in bed, the ulcers of the toes healed and the patient was discharged with the urine free from sugar and diacetic acid, and the blood sugar after fasting 150 mg for each hundred cubic centimeters.

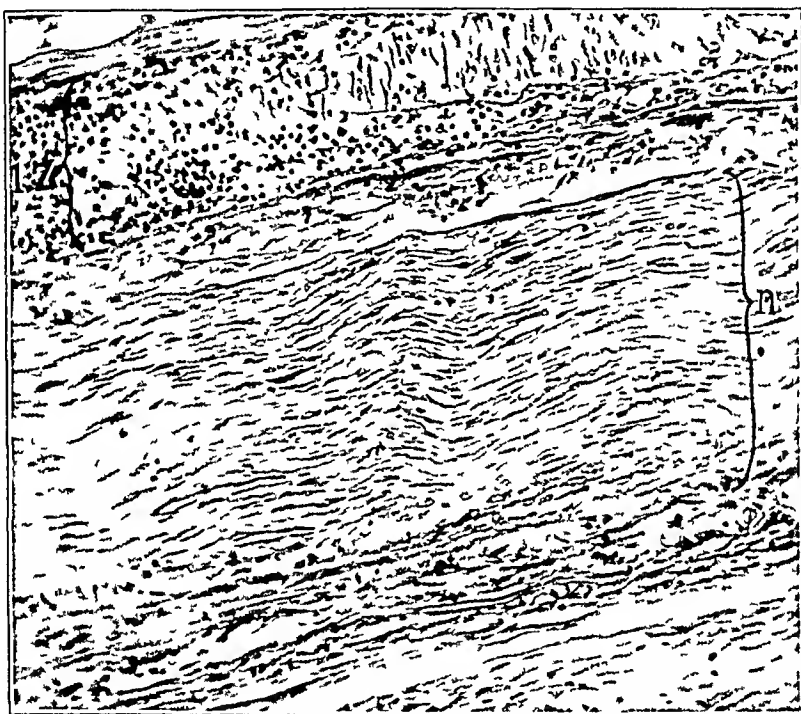


Fig 4 (case 2)—Tibial nerve. Longitudinal section of a nerve bundle, *u*, showing inflammatory reaction, *is*. Van Gieson stain,  $\times 140$ .

The patient was admitted again for gangrene on Feb 4, 1927. In the interval he had followed a weighed diet with reasonable accuracy and had used 10 units of insulin daily. At this time the patient weighed 178 pounds. The urine was free from sugar and the blood sugar was 137 mg for each hundred cubic centimeters. Gangrene affected the middle toe of the left foot. Roentgenograms revealed marked calcification of the vessels of the legs and feet. Examination of the eyegrounds showed moderate fibrosis of the retinal arteries and some punctate degenerative exudates.

On February 7 the middle toe of the left foot was amputated. The patient did well until February 19, when severe infection of the foot developed which spread up the leg as cellulitis. On March 1, the leg was amputated. On March 5, the patient died.

At necropsy cellulitis of the left thigh, slight icterus and hemorrhagic cystitis were found. The spleen was enlarged, it weighed 408 Gm. There was marked sclerosis of the arteries of the foot and thrombosis of the superficial veins. The

spinal cord was not removed. Sections of the peripheral nerves stained poorly by modifications of Weigert's method, but the general structure of the myelin sheaths was fairly well maintained at higher levels. Well marked degeneration, however, was evident more distally from a study of the other sections. Accumulations of fat-bearing cells were seen in the perivascular spaces. The nuclei of the cells of the sheath of Schwann were increased in numbers. There was slight infiltration with polymorphonuclear leukocytes, and more distally rather well marked infiltration with lymphocytes, and of endothelioid cells, chiefly extraneurally (fig 4). The connective tissue was somewhat increased and there was thickening of the arteries in the nerve bundles (fig 5). These changes were marked in the digital nerves, in which normal nerve fibers could not be demonstrated. The muscle

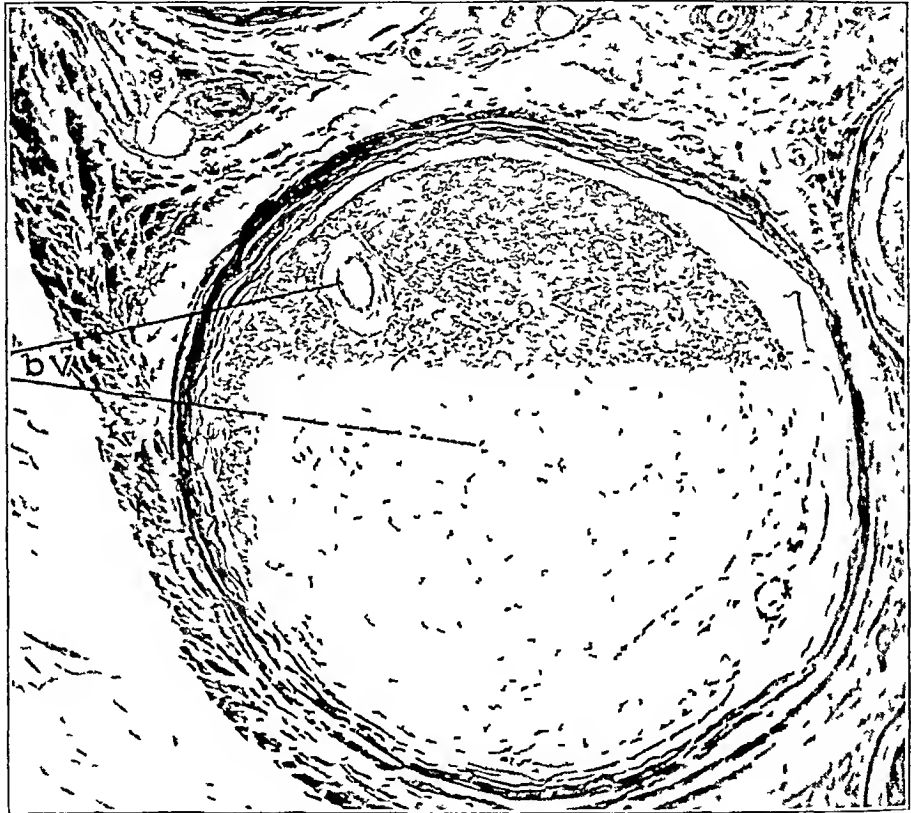


Fig 5 (case 2)—Cross-section of tibial nerve. The degeneration is not so clearly shown at this magnification but the thickened vessels, *bv*, are apparent. Van Gieson stain,  $\times 60$ .

fibers showed numerous fat droplets by the Marchi stain (fig 6). The fibers were swollen and fragmented, the striae were often lost, and there was slight evidence of inflammation.

**CASE 3**—The patient, aged 75, was admitted on May 29, 1923, complaining of cataract in the right eye. There was no record of previous illnesses or of the consumption of alcohol or tobacco.

Examination of the fundi showed questionable primary arteriosclerosis. The blood pressure was 160 systolic and 70 diastolic. A second examination was made in January, 1924, because of a recent cold. Evidences of pneumonia were found. Roentgenographic examination of the chest disclosed consolidation of the right

upper and lower lobes and interlobar pleurisy. Arteriosclerosis was marked. Pulsation of the vessels of either foot could not be palpated. The radial arteries were extremely sclerotic, and roentgenograms of the left leg revealed calcification of the arteries. The urine contained 7 per cent of sugar but not acetone bodies, the blood sugar was 400 mg in each hundred cubic centimeters. The neurologic features of this case were the following. The patient complained of a severe burning, stinging pain of the foot accompanied by marked hyperesthesia and numbness in the posterior portion of the calf of the left leg and left foot. Slight atrophy and fibrillation of the calf of the left leg and of the right anterior tibial group of muscles were noted. Reflexes in both tendo achillis were absent. Cutaneous sensation was normal.

A third examination was made in July, 1925, at which time the patient was admitted with the complaint of gangrene of the three lateral toes of the left foot.

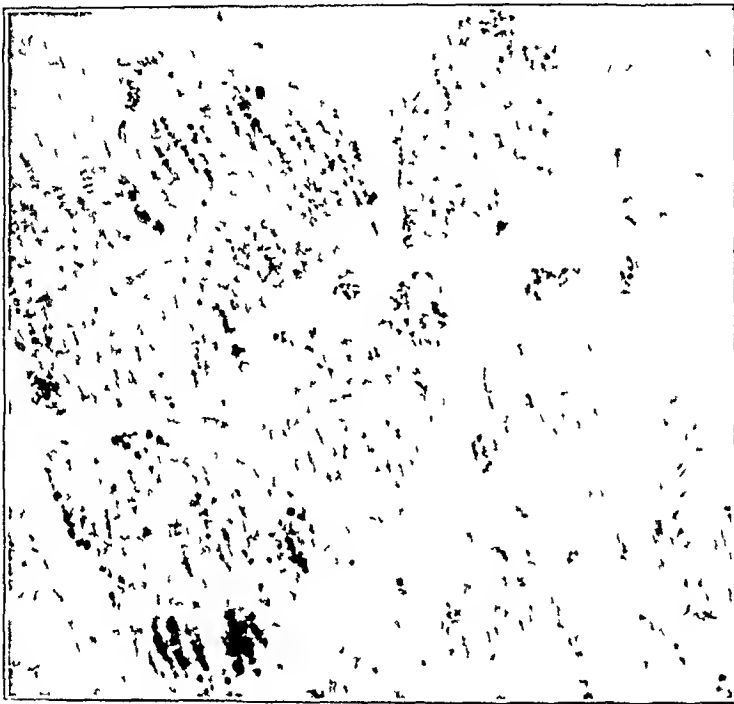


Fig 6 (case 2) —Section of muscle from anterior tibial group. The rows of fat droplets stained black by the osmic acid are the most prominent features of the injured muscle, Marchi stain.

This had begun three months previously. The blood pressure was 240 systolic and 130 diastolic. Diabetes had been mild after recovery from the attack of pneumonia and until recently had been readily controlled by a qualitative diet, without insulin. The left leg was amputated through the knee.

In February, 1927, the left hip was fractured, and the patient was readmitted to the hospital in March in a state of collapse. The urine again contained sugar, granular casts and a large amount of albumin. Death occurred on March 28, at the age of 75, two days after a stroke of paralysis involving the left side.

At necropsy a large, infarcted region was found on the right side of the brain, which contained numerous hemorrhages and polymorphonuclear cells. There was a moderate degree of arteriosclerosis of the smaller vessels. Examination of the spinal cord showed the changes of senility. The cells of the anterior horn were greatly reduced in numbers on one side of the cord in the lower lumbar level.

Unfortunately, the sides had not been marked before embedding, and whether or not these changes corresponded to the side of the amputated limb could not be determined. It will be recalled that fibrillary tremors had been observed in the lower extremities at an earlier examination. These were bilateral and it is unlikely that they were occasioned by disease of the cells of the anterior horn, since those on one side were normal. The hemiplegia had, of course, occurred too recently to have produced any notable results in the tracts of the cord. On the whole, the peripheral nerves appeared to be fairly normal at higher levels. In isolated fibers were some droplets of fat and an occasional fat-laden cell. There was a moderate degree of degeneration in the plantar nerves. The nuclei of the sheath of Schwann were considerably increased in numbers, and there were a few wandering tissue cells. The arteries within the nerves at the levels examined were fairly normal in appearance.

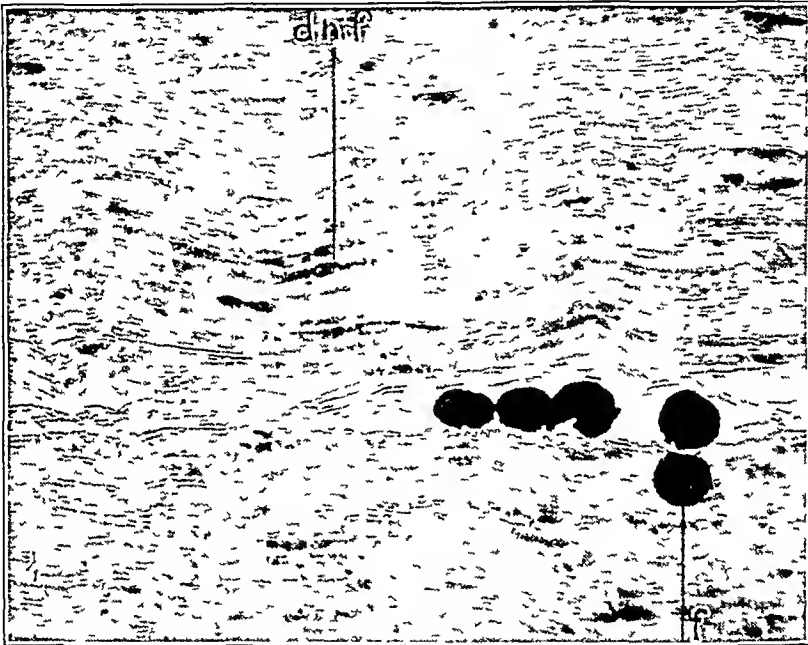


Fig 7 (case 4)—Longitudinal section of femoral nerve. Marchi granules, *dnf*, are stained black in the degenerating nerve fibers, *f*, adventitious fat. Marchi stain,  $\times 75$ .

CASE 4—A housewife, aged 53, first consulted the Mayo clinic on Feb 6, 1928. She complained of soreness of the left lower quadrant of the abdomen, which had been present for twenty-seven years, and sore feet, which she said had felt "like worms jumping in them," for six years. Polyuria and polydipsia had been present since 1925. The urine was examined and glycosuria noted in 1926, but treatment had not been instituted. There had occurred an occasional bloody discharge from the vagina for two years, and soreness had appeared on the toes two years previously. Previous illnesses included pneumonia, sore throat, otitis media and mumps, with no history of syphilis. The patient had not overindulged in the use of tobacco or alcohol. The height was 5 feet and 9 inches (175 cm), the maximal weight, 230 pounds (104.3 Kg), had been reached in 1925.

The weight on admission was 165 pounds (74.8 Kg). Examination revealed an advanced carcinoma of the cervix, with some pelvic infiltration, moderate

peripheral arteriosclerosis and trophic ulcers of the feet. The blood pressure was 140 systolic and 75 diastolic. The dorsalis pedis arteries pulsated normally on both sides. The urine contained a trace of sugar and diacetic acid. The blood sugar was 250 mg. in each hundred cubic centimeters.

Diabetes in this case proved severe, and required the administration of 40 units of insulin daily for its control. The urine became free from sugar under treatment, the ulcers on the toes began to heal, and the patient became markedly improved. The carcinoma was treated with radium, with satisfactory results. On the day before death, an intense abdominal pain developed suddenly and peritonitis followed a perforating gastric ulcer. On exploratory operation, on Feb. 27, 1928, enterostomy was performed. The patient died the following day.

At necropsy diffuse peritonitis was found. The carcinoma had become shrunken to such an extent that it was difficult to find any trace of it. The pelvic nerves were not involved by scar tissue. Sections of the spinal cord and cauda

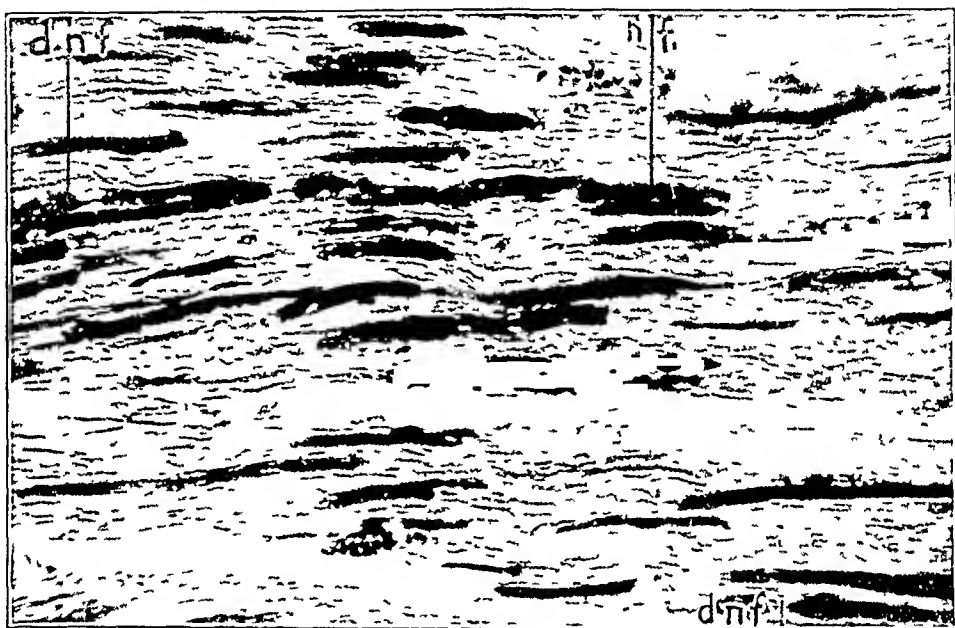


Fig. 8 (case 4)—Tibial nerve. The nerve fibers, *nf*, which are dark in this section are diminished in number. A few of them show vacuolization and other abnormalities, *dnf*. Weigert-Pal stain,  $\times 325$ .

equina were essentially normal. One dorsal root ganglion from the lumbar region showed occasional scattered polymorphonuclear leukocytes and wandering tissue cells. In some of the blood vessels, a larger number of polymorphonuclear cells was seen. In the sciatic nerves was slight arteriosclerosis, and slight degeneration was disclosed by the Marchi method. Both femoral nerves were shown to be slightly degenerated by the Weigert stain, but somewhat more marked degeneration was revealed by the Marchi method (fig. 7). In the tibial nerves, a moderate degree of degeneration was revealed by the Weigert (fig. 8) and Marchi stains, and a moderate grade of arteriosclerosis.

CASE 5<sup>46</sup>—A retired farmer, aged 63, first presented himself at the Mayo Clinic in June, 1922, with the complaint of diabetes mellitus. He had suffered with

<sup>46</sup> In cases 5 to 10 inclusive, only nerves from extremities amputated because of gangrene were available for study. Changes noted here, however, resemble those found in the cases with necropsy so closely that they are included in the series.

cramps in the thighs, calves, feet and hands for ten years. Eight months before, polydipsia had appeared and two months later he had consulted a physician because a nail on his right foot had become black and the toe red, sugar was discovered in the urine at this time. Previous illnesses included nothing more serious than mild influenza in 1918 and occasional tonsillitis. There was no record of syphilis. He had used tobacco with moderation, but he had not used alcohol.

The height was  $63\frac{1}{4}$  inches (160 cm), the maximal weight 163 pounds (74.8 Kg), had been reached in 1909. On admission, the patient weighed 124 pounds (56.2 Kg). He had lost 10 pounds (4.5 Kg) in one month. The blood pressure was 152 systolic and 70 diastolic. The region of the right toenail was infected. The dorsalis pedis arteries pulsated normally. The urine contained a large amount of sugar but did not contain acetone bodies. The blood sugar was 238 mg in each hundred cubic centimeters. The Wasseimann reaction of the blood was negative. Examination of the eyegrounds revealed a few scattered, punctate retinal hemorrhages, slight exaggeration of the retinal arterial reflex and relative venous engorgement. After discharge from the hospital, the patient followed a diet that was rigidly restricted at first and then less restricted, so that the urine contained sugar much of the time.

The patient returned to the clinic in February, 1927. He had done well until seven months before, when the second toe on the left foot had become painful, red and swollen. Examination revealed dry gangrene of the toe, blood pressure of 180 systolic and 90 diastolic and moderate clinical evidence of arteriosclerosis. There were some structural blurring in the nasal portion of the disk of the right eye, a number of scattered retinal hemorrhages and a group of points of exudate. The urine contained sugar but did not contain diacetic acid. The fasting blood sugar the following morning, after a dose of 10 units of insulin the night before admission, was 129 mg in each hundred cubic centimeters. The leukocyte count was 14,800 in each cubic millimeter of blood, the blood urea was 37 and the blood sugar, 129 mg in each hundred cubic centimeters. The carbon dioxide-combining power was 50 per cent. The tendon reflexes were elicited with difficulty.

The gangrenous toe was amputated in March, 1927. The wound failed to heal, and on March 10, the left leg was amputated below the knee. The wound again failed to heal and on March 21 another amputation was made at the middle third of the left thigh. The third operation was followed by satisfactory healing. During this period, the urine occasionally contained sugar and diacetic acid. For the most part, however, diabetes was rigidly controlled despite the infection, so that the blood sugar ranged from 196 to 93 mg in each hundred cubic centimeters.

The nerves removed from the higher levels of the amputated limb showed from slight to moderate degeneration. In some of the bundles, however, there was marked destruction. There was marked arteriosclerosis of the vessels in the nerves. At higher levels there was a moderate amount of infiltration with small round cells and polymorphonuclear leukocytes. This was not present more distally. Nerves from the peripheral parts of the limb were markedly degenerated and the digital nerves were completely degenerated, as shown by stained preparations of myelin sheath and axis cylinders. Replacement had been made by connective tissue. There was a moderate degree of degeneration of muscle fibers, fibers were swollen, there was some increase in the number of nuclei, and an accumulation of fine fat droplets in the fibrils, as shown by the Marchi stain.

CASE 6—A farmer, aged 64, was admitted to the Mayo Clinic on Feb 20, 1923, with complaints of gangrene of the left foot and diabetes. Sugar had been discovered in the urine in 1917 and had not been absent since that time. One month before admission, the left great toe had begun to tingle, had become tender but not

painful and presently had become gangrenous. Previous illnesses included only a mild attack of rheumatic fever. There was no history of syphilis. The use of alcohol and tobacco had been moderate. The height was 65½ inches (166.3 cm). The maximal weight reached 174 pounds (78.9 Kg).

The patient was pale, somewhat emaciated and extremely emphysematous, and the weight was 157 pounds (72.1 Kg). The left great toe was completely gangrenous. The popliteal arteries pulsated normally, but pulsation could not be felt in either dorsalis pedis artery. The blood pressure was 98 systolic and 60 diastolic. The eyegrounds appeared normal. The urine contained sugar and a trace of diacetic acid. The fasting blood sugar was 240 mg in each hundred cubic centimeters. The Wassermann reaction of the blood, if it was determined, was



Fig 9 (case 6) —Digital nerve, *n*, and vessel, *bv*. The nerve contains a few dark points which suggest normal myelin sheaths, but none of these proves to be such on closer inspection. The sclerotic vessel nearby is clearly shown. Weigert-Pal stain,  $\times 150$ .

not recorded. Diabetes proved to be difficult to control, and as much as 60 units of insulin were required, together with a rigid diet, to check glycosuria completely. On February 26, the left leg was amputated through the upper third. A second amputation through the middle of the thigh was necessary on March 5. Healing following the second operation was satisfactory. In April, large carbuncles appeared over the sacrum and lower lumbar region. These were cauterized, resulting in large ulcers which gradually healed. The patient died at his home in diabetic coma on July 4, 1923, as a result of neglect. He had been doing well, but following a family quarrel, his wife had refused either to prepare his meals or to give him insulin.



There was rather well marked degeneration of the nerves at higher levels, as disclosed by all stains used, and there was complete degeneration in the digital branches (fig 9). The axis cylinders appeared to be fairly normal at higher levels, where there was thickening of the perineurium. The nuclei in the course of the nerves were very much deformed and some of them were extremely attenuated, in other instances they were fragmented, bent, constricted and pyknotic. There was slight infiltration of the perineural tissues with polymorphonuclear leukocytes and wandering tissue cells. The vessels of the toes were very much thickened. The muscles removed from the plantar aspect of the foot showed some vacuolization, fragmentation, increase in the number of nuclei and, in other places, outright necrosis.

CASE 7—The patient, a janitor, aged 57, was admitted to the Mayo Clinic on May 15, 1923, with complaints of diabetes and of gangrene of the toes. Ten years previously, he had lost weight and strength and had suffered from polyuria and polydipsia. These symptoms had led to examination of the urine, sugar was discovered and a diet instituted, which had been followed fairly faithfully. Two years prior to admission, after numbness had been noted in the feet, gangrene had set in in the left toes. Recovery from this was satisfactory, with subsequent healing. Four weeks before admission, gangrene had recurred. Previous illnesses included only some attacks of tonsillitis years before. There was no history of syphilis. The maximal weight was not recorded.

On examination, general arteriosclerosis, gangrene of the left toes, hypertension and myocardial degeneration were found. Roentgenograms disclosed destruction of the first and second phalanges of the left great toe, other roentgenograms showed thickening of the pleura in the right lower part of the chest. The eye-grounds contained numerous exudates and hemorrhages around the macular regions, more marked on the right. The picture was that of central punctate retinitis of the diabetic type. The urine contained sugar but did not contain diacetic acid, the fasting blood sugar was 317 mg in each hundred cubic centimeters. The Wassermann reaction of the blood was negative. Treatment was instituted, and on June 7, the left leg was amputated through the upper third. Convalescence was satisfactory, and the patient was strong and well, without complaining of pains in the leg when last heard from in June, 1926. All of the nerves studied displayed marked degeneration and marked arteriosclerosis, the intensity of these characteristics was more marked peripherally. A slight degree of small round cell infiltration was noted in one section.

CASE 8—The patient, a farmer's wife, aged 58, was admitted to the Mayo Clinic on Feb 4, 1927, with complaints of diabetes and gangrene. Seven years previously, polyuria, polydipsia, general weakness, especially in the lower extremities, and a carbuncle over the lumbar region had led to general examination and to the discovery of sugar in the urine. A diet had been instituted at that time. Insulin had been used for eight weeks. Previous illnesses included only occasional attacks of tonsillitis. There was no reason to suspect syphilis. Alcohol and tobacco had not been used. The height was 5 feet 1½ inches (156 cm), and the maximal weight, 210 pounds (95.2 Kg), had been reached at the age of 40. Five months prior to admission, the fourth toe on the left side had become infected and had refused to heal. The patient further complained of irritation of the external genitalia, and numbness of the right arm and legs when she was fatigued.

Examination revealed a body weight of 167 pounds (75.7 Kg), and gangrene of the third and fourth toes of the left foot. Calcification of the vessels of the legs was revealed by roentgenograms. The right ocular fundus contained hemor-

rhages and areas of degeneration, the left fundus was obscured by cataract of the lens. The urine did not contain sugar or diacetic acid but contained much pus. The fasting blood sugar was 153 mg in each hundred cubic centimeters, later this figure rose to 217 mg. The blood urea was 36 mg, and the carbon dioxide combining power was 58 per cent by volume. The Wassermann reaction of the blood was negative. Neurologic features were as follows: absence of tendo achillis and patellar reflexes, diminution of tactile, vibratory and joint sensibilities, moderately on the left foot, more noticeably on the right, moderate incoordination of both lower extremities, tenderness of the calves of both legs, and increase in the size of the left peroneal nerve where it passed over the head of the fibula.

The diabetes in this case proved to be rather mild and was readily controlled with a careful diet and small doses of insulin (from 10 to 20 units), in spite of infection accompanied by a temperature at times as high as 103 F, and by leukocytosis. On February 14, the third and fourth toes of the left foot were amputated. On March 7, the left leg was amputated at the upper third, and on March 21, the leg was reamputated at the middle of the thigh. The wound again failed to heal, and the patient died on May 19, 1927. Necropsy was not obtained.

A study of the peripheral nerves in the amputated leg showed marked degeneration at higher levels, and there was complete disintegration and a general loss of architectural arrangement distally. The nuclei of the neurilemma were considerably increased in numbers. Wandering tissue cells were present in moderate numbers, both in the nerves and in the surrounding areolar tissue. There was some ballooning, and here and there the staining of the myelin sheaths was interrupted and vacuolization was noted. Arteriosclerosis was moderate above and marked below. In the peroneal nerve, one of the arteries was calcified and contained a canalized thrombus. The digital nerves were completely degenerated, some of the adjacent blood vessels were thrombosed. The connective tissue was moderately increased. The Marchi stain did not show accumulation of fat, however, fat was noted in sections stained with scharlach r. The muscles of the calves of the legs were fairly normal, however, there was some longitudinal splitting of the fibers, disappearance of the striae and increase in the number of nuclei.

CASE 9—The patient, an attorney, aged 71, consulted the Mayo Clinic on March 15, 1927, with complaints of gangrene of the left foot and kidney trouble. Four or five years previously, he had had nocturnal frequency of urination. Two weeks before admission a callus appeared under the toes of the left foot, this became infected later, the toe turned black and the back of the foot became red. There had also been some polydipsia recently. Previous illness included two attacks of influenza and one each of gonorrhea, pleurisy and syphilis. A secondary rash was noted at the age of 40, a primary rash had not been noted. There had been moderate indulgence in alcohol and tobacco.

The patient was 6 feet in height and weighed 180 pounds (81.6 Kg). His previous maximal weight was not recorded. The blood pressure was 120 systolic and 80 diastolic. Examination of the eyegrounds revealed peripheral pigmentary degeneration of the choroid, of the senile type. Roentgenograms of the left foot showed hypertrophic arthritis of the metatarsophalangeal joint, and marked calcification of the vessels. The left great toe was affected with dry gangrene. The dorsum of the left foot was reddened and warm. The leukocyte count was 22,200 in each cubic millimeter, the Wassermann reaction of the blood was strongly positive on two occasions. The urine contained a trace of sugar but did not contain diacetic acid. The blood sugar was 172 mg in each hundred cubic centimeters.

Three or four colonies of *Streptococcus viridans* appeared in the blood cultures made on March 18, but growth was not evident in the culture made March 19. The left leg was amputated on March 17, through the lower third of the thigh. Healing was unsatisfactory and reamputation was done on April 9 through the middle third of the thigh.

The sciatic nerve did not stain well with modification of Weigert's stain, but by other methods from slight to moderate degeneration was noted. Distally, the nerves were greatly altered. There was moderate arteriosclerosis above, and more marked arteriosclerosis below. The connective tissue was somewhat increased, and a moderate number of wandering tissue cells was noted. The cells of the neurilemma were increased in number and distorted to a moderate degree. The muscle showed rather marked degeneration with the Marchi stain, the fibers were irregular in size, and the striae could not be seen in places.

CASE 10—A farmer, aged 72, was admitted to the Mayo Clinic on May 23, 1927, with complaints of gangrene and diabetes. Six months previously, a horse had stepped on his left great toe and a few days afterward, a block of wood had fallen on the same toe. The resulting infection failed to heal, and led to gangrene. Polyuria had been noted a year previously, but sugar had been found for the first time when a physician's advice was sought because of the injured toe. A diet restricted qualitatively in carbohydrate had been followed since then. A daughter had diabetes and a brother had died from arteriosclerosis. There was no history of venereal infection. Previous illnesses included tonsillitis at the age of 37 and appendicitis at the age of 57. Alcohol had been used rarely, and tobacco moderately (one box of snuff each week). The maximal body weight, 210 pounds (95.2 Kg), had been attained at the age of 67.

The height was 5 feet and 4 inches, the weight was 151 pounds (68.5 Kg). The blood pressure was 138 systolic and 90 diastolic. There was moderate pyorrhea and some evidence of arteriosclerosis. Pulsation could not be palpated in the arteries of either foot or in the popliteal arteries. The toes of both feet were bluish when the legs were dependent. There was gangrene of the first left toe. The eyegrounds revealed rather small arteries and moderate retinitis of the central, punctate, diabetic type. Large plaques appeared in the macula of the left eye and smaller exudates in the right macula. Formation of new vessels was noted in the left disk, and opacity of the lens was present in both eyes. Roentgenographic examination revealed hypertrophic arthritis of the ankles. The urine contained a small amount of sugar, a trace of albumin and a few erythrocytes and leukocytes. The blood sugar was 195 mg in each hundred cubic centimeters. The Wassermann reaction of the blood was negative. Diabetes in this case proved relatively mild and could be controlled by dietetic management alone. The left leg was amputated above the knee, where the vessels were found to pulsate but were very much thickened. A study of the nerves disclosed moderate degeneration at higher levels and rather marked degeneration peripherally. Here the sections stained by the method of Orlandi together with scharlach r showed not only marked degeneration, but delicate tenuous fibrils obviously in a stage of regeneration. There was moderate arteriosclerosis of the vessels within the nerves which was more marked distally. Wandering tissue cells in moderate numbers were seen peripherally in the nerve and its sheath. The nuclei of Schwann's cells were irregular, elongated, some of them pyknotic and others vacuolated. The muscle fibers were very wide, pale and fragmented, had lost their striations and were obviously rather markedly degenerated.

## COMMENT

The ten cases reported were selected for study more because of availability of neurologic tissues for histologic examination than because they were especially good examples of diabetic neuritis. Although in cases 1 and 8 the neurologic complications were sufficiently complex to justify a diagnosis of pseudotabes diabetica, few of the other patients exhibited more than mild pain or paresthesia and none any ataxia or motor weakness. The extent of degeneration found in the peripheral nerves in all ten cases is the more remarkable, in view of the mildness of nerve symptoms. It would appear that accurate correlation does not exist between the degree of degeneration of the nerves and the symptoms.

The degeneration noted in the three spinal cords examined was slight, and most of this could readily be explained on the basis of senility and arteriosclerosis. When the clinical features of cerebrospinal arteriosclerosis are subtracted from those noted there is a residuum which cannot be accounted for on the basis of the changes noted in the spinal cords. We are unable to agree with the view of Sandmeyer and others that the degeneration of the spinal cord is of the type seen in pernicious anemia. The clinical picture in these cases was also totally unlike that of subacute combined degeneration of pernicious anemia. We have not encountered such a case ourselves, except in five cases in which the two diseases, pernicious anemia and diabetes, were associated. One gains the impression that the lateral columns are seldom, if ever, involved by diabetes, and that the mechanism in the production of the lesions reported as occurring in the posterior columns must be different from that active in pernicious anemia. The reports of Williamson<sup>19</sup> and Schweiger are the most convincing in this respect.

The degeneration of the nerves was extensive in eight cases, and less marked in two. It was usually diffuse, but in two cases it was patchy and involved isolated bundles of fibers lying in the midst of relatively normal bundles. This is not seen in the usual cases of toxic neuritis. Whether or not it was only a coincidence we cannot say, but it was only in these two cases that the diagnosis of pseudotabes diabetica could be made. Associated with it in all but one case was marked thickening of the walls of the intraneural vessels. Cellular infiltration, usually slight, was present in nine of the cases. The perineurium was thickened in all but one case. The muscles showed a rather marked degeneration in the six cases in which the muscles were studied.

In the ten cases studied it does not seem likely that acidosis was a factor of any etiologic significance. Many of these patients were under reasonably careful management. The diabetes in all of them was mild or moderate, and acetone was seldom found in the urine. Similarly, there is little reason to believe that sugar in the blood played much of a part. It is true that the blood sugar was elevated in all of the cases, but

it was not excessively high in any of them, and the urine was free from sugar in most of the cases most of the time. Furthermore, if acetone bodies or sugar produce neuritis, we should expect to encounter more neuritis in groups of patients with severe diabetes, this is not our clinical experience. The severest diabetes occurs as a rule in young patients, and such patients seldom manifest neuritis. Indeed, if we exclude from consideration the pains of acidosis (precoma pains) which promptly disappear when acidosis is brought under control, young persons with severest diabetes practically never complain of pain, paresthesia or other neurologic symptoms. Although the patients with severest diabetes are usually young, we have also seen a great many cases of severe diabetes in older patients uncomplicated by neurologic symptoms.

In the individual case one is never certain that some complicating infection or toxin may not be responsible for neuritis, but when large groups of patients with diabetes are compared with groups of patients with other chronic disease, for instance tuberculosis, one is struck by the fact that neuritis occurs with much greater frequency in the group of patients with diabetes. This should not be the case if complicating infections were responsible. In the ten cases included in this study, syphilis was present in only one, and other complicating infection or intoxication was not sufficiently in evidence to explain the neuritis encountered.

Striking clinical dissimilarity between neuritis of diabetes and that produced by alcohol, lead, diphtheria and other common causes of neuritis is the almost exclusive predilection in diabetic neuritis for sensory disturbances. Pain, paresthesia, and areflexia are the more important characteristics. Lack of the usual sensitivity of nerve trunks and muscles and marked predilection for involvement of the lower extremities are also characteristic. Motor lesions are rare, although peroneal palsy from injury of the nerve by crossing the legs and crutch palsy are not uncommon, the nerve trunks, it would seem, are more vulnerable than normally. Like "the crossed leg" paralysis of nondiabetic patients, the peroneal palsy of diabetes is much more common in men.

That atherosclerosis of the nutrient vessel of the nerves plays a leading part in the production of diabetic neuritis appears to be highly probable. In each of the ten cases described in this report, marked arteriosclerosis was present as a complication. The patchy character of the lesions in the nerves in some cases and the marked thickening of the walls of the intraneural vessels are consistent with the idea that arteriosclerosis and the resulting ischemia of nervous tissue were factors of significance. In practically all of our clinical cases of diabetic neuritis and in all reported here, clinical evidence of complicating arteriosclerosis is at hand. The description of the so-called arteriosclerotic and senile neuritis that is observed in subjects free from diabetes coincides

well with what we observe in diabetic neuritis<sup>47</sup> The digital nerves studied by Mahornei<sup>48</sup> in cases of Bueiger's disease in which ischemia is certainly present, show similar necrosis of isolated nerve bundles On the other hand, as has been stated, there is not an accurate correlation between the degree of degeneration of the nerves and the symptoms The subject deserves attentive consideration, and it is to be hoped that additional histologic material from cases intensively studied during life may be subjected to examination

#### SUMMARY AND CONCLUSIONS

1 Diabetic neuritis is mainly a sensory disturbance without corresponding motor impairment, pain, paresthesia and areflexia are its main characteristics It shows also a marked predilection for the lower extremities

2 The histologic material from ten cases studied clinically is described Two of these cases are instances of diabetic polyneuritis In these two cases, isolated bundles of nerve fibers were necrotic

3 The degeneration noted in the spinal cord is relatively unimportant, and it is doubtful whether it could explain the clinical data The lesions in the spinal cord do not bear resemblance to those found in combined degeneration of the cord seen in pernicious anemia

4 The most significant lesions are those of the nerve trunks These are associated in nearly all cases with marked thickening of the walls of the intraneural vessels The degeneration is more marked toward the periphery

5 There is good reason to believe that neither glycosuria nor acidosis plays a direct part in the production of diabetic neuritis In the ten cases studied, syphilis could be diagnosed in only one, and other complicating infections and intoxications such as those caused by alcohol and certain metals were not sufficiently in evidence to explain the neuritis

6 The results of this study lend support to the opinion that the factor of greatest significance in the lesions of the nerves found in diabetes mellitus is atherosclerosis

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47 Gombault, Albert Note sur l'état du nerf collatéral extrême de gros orteil chez le vieillard, *Bull Soc anat de Paris* **4** 410, 1890 Lapinsky, Michael Zur Frage der Veränderungen in den peripherischen Nerven bei der chronischen Erkrankung der Gefässe der Extremitäten, *Deutsche Ztschr f Nervenhe* **13** 468, 1898 Oppenheim, Hermann Ueber die senile Form des multiplen Neuritis, *Berl klin Wchnschr* **30** 589, 1893 Joffroy, A, and Achard, C Nevrite périphérique d'origine vasculaire, *Arch de méd exper et d'anat path* **1** 229, 1889, Gangrene cutanée du gros orteil chez un ataxique, *considerations sur le rôle de la nevrite périphérique dans l'ataxie*, *ibid* **1** 241, 1889 Schlesinger, Hermann Ueber eine durch Gefässerkrankungen bedingte Form der Neuritis, *Neurol Centralbl* **14** 578 and 634, 1895, Die Sehnen- und Hautreflexe an den unteren Extremitäten bei alten Leuten, *Deutsche Ztschr f Nervenhe* **47-48** 710, 1913

48 Brown, G E, Allen, E V, and Mahornei, H R *Thrombo-Anguitis Obliterans*, Philadelphia, W B Saunders Company, 1928 p 40

# MASSIVE PULMONARY ATELECTASIS (COLLAPSE)

ITS PROBABLE MECHANISM AND CLINICAL SIGNIFICANCE \*

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Since Pasteur's<sup>1</sup> original study of this phenomenon as a postdiphtheritic and postoperative complication, this subject has been receiving increasing attention. Numerous case reports and reviews have appeared containing many observations on the etiology, incidence and mechanism of this phenomenon. Its probable mechanism has particularly interested the various authors, and various theories have been advanced to explain it. I shall report five additional cases of massive pulmonary atelectasis. One of these was studied in considerable detail over a period of years, and presents some unique features not previously reported. All the cases illustrate the various factors which are responsible for this phenomenon, suggesting its probable mechanism, and emphasizing its clinical significance.

## DEFINITION AND CLASSIFICATION

By massive collapse, atelectasis or apneumotosis is understood the deflation of large portions of lung tissue to a retracted airless state. While these terms are frequently used interchangeably, Scott, Pancoast, Jackson<sup>2</sup> and others prefer the term atelectasis as one which describes the condition of deflation of the alveolar tissue more accurately. They would reserve the term collapse of the lung for the condition resulting from positive intrapleural pressure, as in pneumohydropyothorax, in which there is not only deflation of the alveolar tissue but also collapse of the bronchi. No such differentiation is tenable or advisable at this time. In the cases reported by Packard,<sup>3</sup> collapse of the bronchi was assumed to be present in all cases of massive collapse, and he uses this as a differential point in the diagnosis of pulmonary collapse and pulmonary fibrosis. In the latter condition, this author claimed the bronchi remain patent, while in massive collapse they are collapsed.

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\* From the Medical Department of the New York Post-Graduate Medical School and Hospital, service of Dr. R. H. Halsey

1 Pasteur, W. Massive Collapse of the Lung, *Brit J Surg* **1** 587 (April) 1914

2 Jackson, C., and Lee, W. E. Acute Massive Collapse of the Lungs, *Tr Am Surg A* **43** 723, 1925

3 Packard, E. N. Massive Collapse (Atelectasis) Associated with Pulmonary Tuberculosis and Tumor *Am Rev Tuberc* **18** 7 (July) 1928

Massive pulmonary collapse or atelectasis has been observed in a great variety of clinical conditions. Pasteur<sup>1</sup> observed it as a complication in nasal and pharyngeal diphtheria, and believed it to be due to diaphragmatic paralysis. Later he found many examples of this condition as a postoperative complication in abdominal cases. Since then numerous reports have appeared in the literature. Bradford<sup>4</sup> found it in about 10 per cent of all persons suffering from nonpenetrating injuries of the thoracic wall. Others reported similar accidents complicating injuries to the pelvis, buttocks and thighs. There are also cases on record in which massive pulmonary collapse was found as a complication in acute diaphragmatic pleurisy and in pneumonia. Its occurrence with foreign body obstructions of the bronchi has been studied particularly by Jackson and his associates, and recently it was described by Packard<sup>3</sup> and others in connection with obstructing endobronchial neoplasm, retained blood clots following pulmonary hemorrhage, as well as a complication of pulmonary tuberculosis.

Various classifications of this condition have been suggested, but none appear satisfactory. An analysis of the clinical types of massive collapse from the point of view of their probable mechanism will probably prove most helpful in the study of the subject.

#### THE MECHANISM OF MASSIVE COLLAPSE

The earliest observations on massive pulmonary atelectasis were made in the new-born infant, so-called congenital atelectasis. At birth, the alveolar walls are in close contact and the lungs are solid organs. With the first respirations, the lungs undergo gradual expansion, the alveoli, bronchioles and bronchi rapidly assuming their permanent form. Failure to do so results in partial or complete pulmonary atelectasis. A form of congenital atelectasis not infrequently met with is that due to accumulated secretions occluding the bronchial tree of the infant and preventing the normal inflation of the lungs. It is a common practice of the obstetrician to restore normal respiratory function by aspirating these secretions. This type of case represents the simplest mechanism of massive pulmonary atelectasis, namely, that due to gross and manifest bronchial occlusion.

Congenital atelectasis is also found in infants with congenital syphilis or with lesions of the central nervous system, as well as in those who are premature or congenitally weak. This type of atelectasis is apparently due to interference with normal respiratory movements. It has been observed in some of these infants that, as a result of the weakness of the intercostal muscles, during inspiration, when the diaphragm descends, the thoracic cavity instead of enlarging, recedes, is sucked in,

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4 Bradford, J. R. Massive Collapse of Lungs, *Quart J Med* **12** 127, 1918



so to speak, maintaining the underlying lung in a state of partial or complete atelectasis. Portions of the lung in these congenitally weak infants may remain atelectatic during the first year of life. A similar mechanism is probably operative in weak, cachectic or moribund persons in whom smaller or larger areas of atelectasis, especially at the margins and bases of the lungs, are of frequent occurrence clinically and post-mortem.

A careful analysis of the clinical and experimental data at hand suggests that, from the point of view of the probable mechanism, most of the cases of acquired massive pulmonary atelectasis can be classified into three main groups.

**Group 1** Cases in which gross bronchial obstruction is the manifest cause of the condition.

**Group 2** Cases in which the primary factor is an interference with the proper respiratory movements, with which is associated increased bronchial secretion and a suppression of the cough reflex. The accumulated and retained secretions eventually lead to bronchial occlusion with resulting atelectasis.

**Group 3** Cases in which extrabronchial pressure leads to partial stenosis, the complete occlusion probably being due either to mucosal tuigescence or to bronchial spasm, associated with plugs of retained inspissated secretions.

In all these cases, following the bronchial occlusion, the alveolar air is absorbed by the pulmonary circulation and atelectasis results.

*Mechanism of Massive Pulmonary Atelectasis Due to Gross Endobronchial Obstruction*—This group includes the large number of cases in which obstruction in the bronchus is due to an opaque or nonopaque foreign body, to endobronchial neoplasm, to retained blood clots, to aspirated diphtheritic membrane, etc.

The mechanism involved with foreign body obstruction has been studied extensively by a great many workers and particularly by Chevalier Jackson and his associates at his bronchoscopic clinic where they have seen hundreds of such cases. This author recognizes three types of bronchial obstruction.

**1 By-Pass-Valve Obstruction** This type is a partial obstruction which permits both ingress and egress of air past the obstruction and which does not cause either collapse or emphysema of the tributary lung.

**2 Check-Valve Obstruction** This type allows the air to pass in during inspiration, when the bronchial diameter is increased, but prevents the egress of air from the alveoli during expiration. This will occur when the obstructing object is just large enough to produce complete occlusion of the bronchus when the diameter is decreased during expiration. As a result of this mechanism the air content of the alveoli is progressively increased, eventually producing obstructive emphysema.

3 Stop-Valve Obstruction In this type the air cannot get in during inspiration or out during expiration. Following this the alveolar air is absorbed by the pulmonary circulation and atelectasis results.

While this last mechanism has been reported most frequently in cases of all kinds of nut kernels in the bronchial tree, it has been seen in many others in which plugs of tough secretions or of diphtheritic membrane act as the occluding agent. Jackson, after careful study of a large series of cases, came to the conclusion that most, if not all, instances of so-called post-tracheotomy pneumonia were instances of massive pulmonary atelectasis resulting from bronchial obstruction by inspissated crusts of secretions or of diphtheritic membrane. He repeatedly demonstrated that the signs of pneumonia would clear up in a few minutes following bronchoscopic aspiration of these obstructions from the bronchi. It is Jackson's opinion that the postdiphtheritic pulmonary collapse reported by Pasteur and others, and believed by them to be caused by respiratory paralysis, may in reality have been instances of bronchial obstruction by diphtheritic exudate. At any rate, in his clinic the routine removal of these obstructing exudates from the bronchi has prevented the occurrence of massive pulmonary atelectasis as a post-diphtheritic complication.

An endobronchial neoplasm may similarly produce bronchial obstruction, with resulting massive pulmonary atelectasis, the mechanism being analogous to the one just described. Packard<sup>3</sup> included in his reports one such example. Wessler and Jaches<sup>5</sup> described an interesting case of massive pulmonary atelectasis resulting from bronchial occlusion by a benign tumor. After the removal of the tumor with the aid of the bronchoscope, the entire clinical picture, which had lasted several months, cleared up with remarkable rapidity. Such instances are probably more frequent than the relatively few reports in the literature would lead one to believe. The atelectasis resulting from this type of pulmonary occlusion, when relatively circumscribed, is undoubtedly taken for extensive tumor infiltration. However, a more careful study of the physical and roentgen signs in this type of case, with bronchoscopic examination, would readily establish the correct diagnosis.

Similarly, the retained clot after a brisk pulmonary hemorrhage may cause bronchial occlusion with resulting massive atelectasis. Such a case has been reported by J. L. Wilson<sup>6</sup> in which the diagnosis was established by physical and roentgen examination and confirmed by the recovery of the expelled blood clots in the form of bronchial casts, following which all signs and symptoms cleared up.

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5 Wessler, H., and Jaches, L. *Clinical Roentgenology of Diseases of the Chest*, Troy, N. Y., The Southworth Company, 1923, p. 51.

6 Wilson, J. L. Hemoptysis in Tuberculosis Followed by Massive Pulmonary Atelectasis, *Am Rev Tuberc* **19** 310 (March) 1929.

The following is a brief report of a similar case observed by me about two years ago

CASE 1—Mrs M C, aged 29, had her initial hemoptysis about ten years before when her condition was first diagnosed as one of bilateral apical pulmonary tuberculosis. Since then she had had two more hemoptyses, one four years and the other four weeks before the occurrence of the present episode. After each attack of hemoptysis she recuperated quickly, showing no extension of the pathologic process in the lungs, and being free from local and constitutional symptoms between the attacks. From her attending physician, I learned that the physical signs in the chest had for years been limited to the apexes on both sides.

On the day following the last hemoptysis, a critical condition suddenly developed. The patient appeared acutely ill, with a temperature of 103 F, marked dyspnea and slight cyanosis. The attending physician called my attention to the fact that shortly following the hemoptysis there had occurred a sudden and marked change in the physical signs in the left lung which he interpreted as those of extensive tuberculous pneumonia. The physical signs in the chest at that time were striking. The left hemithorax was retracted and relatively immobile, tactile fremitus was diminished or absent over the lower half, the percussion note was dull to flat over the upper half and markedly flat over the lower half, the breath sounds were of bronchial quality over the upper lobe and diminished or absent over the rest of the lung, no rales were heard. On the right side, the respiratory movements were exaggerated and the apex showed evidence of old infiltration. The cardiac apex beat could be seen and felt in the fourth left interspace near the anterior axillary border. The trachea was deviated to the left. The diaphragmatic movements could not be determined because of the serious condition of the patient.

The history, clinical picture and physical signs suggested the diagnosis of massive pulmonary atelectasis due to bronchial occlusion by a blood clot and involving the major portion of the left lung. Because of the likelihood that the blood clot was infected, a guarded prognosis was given.

The patient's condition continued to be serious, though she appeared less uncomfortable the next day. On the third day, and about seventy-two hours following the onset of the bronchial obstruction, she had a severe spell of coughing followed by what appeared to be another hemoptysis, which consisted of blood clots mainly, and which subsided after a short period of time. When I saw her about one hour later, she appeared entirely comfortable. Physical examination of the lungs at this time revealed improved resonance, fairly normal breath sounds and numerous rales over the left hemithorax. The cardiac apex and trachea appeared to have returned to their normal position. Within the next four days the symptoms subsided, and the signs in the chest were once again only those of bilateral apical tuberculosis.

This was an instance of massive pulmonary atelectasis resulting from bronchial obstruction by a blood clot which was spontaneously relieved after coughing up of the occluding clot. The suddenness of the onset of the symptoms, the characteristic physical signs and the rapidity with which the entire clinical picture cleared up after the removal of the obstruction are particularly noteworthy.

*The Mechanism of Massive Atelectasis Due Primarily to an Interference with the Nervous or Muscular Mechanism of Respiration*—In

this important and large group of cases are included all those which have been observed as a postoperative complication following upper abdominal manipulations, as well as those occurring with paretic or paralytic states of the muscles of respiration

In connection with the probable mechanism involved in the production of massive atelectasis in this type of case, many interesting observations have been made. Martin and Haie, as quoted by Pasteur,<sup>1</sup> were able to produce in animals complete bilateral pulmonary atelectasis by section of both phrenic nerves. Briscoe<sup>7</sup> reported three observations of complete bilateral pulmonary deflation in patients with high cervical spinal paralysis. In the surgical treatment of pulmonary tuberculosis by unilateral phrenectomy, atelectasis of the lower lobe is readily accomplished. Pearson Liwine, quoted by Jackson and Lee,<sup>2</sup> observed atelectasis of the upper lobe in a patient with diphtheritic paralysis of the thoracic muscles. In all these instances, paralysis of the muscles of respiration resulted in corresponding deflation of the pulmonary tissue.

A similar case has been observed by me in a patient with alcoholic polyneuritis.

CASE 2—This patient, who, in addition to extensive polyneuritis with involvement of the intercostal muscles, was also suffering with acute bronchitis, suddenly developed severe suffocating dyspnea and a state of shock. When seen a short time later, he presented the characteristic clinical picture of acute massive atelectasis involving most of the left lung. He appeared to be in a state of shock, with marked dyspnea as the outstanding symptom. The involved left hemithorax seemed shrunken and immobile, the trachea and heart were deviated toward the involved side, breath sounds were absent at the base and harsh over the upper lobe and no râles were elicited. There was hyperresonance and evidence of bronchitis in the right lung. With the aid of emetics and expectorants, the condition cleared up spontaneously within a few hours.

In this case the mechanism is somewhat more intricate. The primary cause appeared to be the weakness of the intercostal muscles incidental to the existing polyneuritis. An important contributing factor was the patient's habit of lying on his left side, thus favoring the immobilization of the diaphragm on that side. This interference with the respiratory function undoubtedly resulted in partial atelectasis of the underlying pulmonary tissue. As a result of the existing bronchial catarrh, there was extensive bronchial secretion, owing to muscular weakness of the patient, the cough was ineffective in clearing out the secretions as rapidly as they formed, so that they accumulated to a degree sufficient to act as occluding plugs in the bronchi. With the development of complete bronchial occlusion, gradual absorption of the alveolar air by

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<sup>7</sup> Briscoe, J. C. Mechanism of Post-Operative Collapse. *Quart. J. Med.* 12: 27, 1918.

the pulmonary circulation took place with resulting massive atelectasis Elliott and Dingley,<sup>8</sup> after a careful study of the subject, concluded that such a mechanism is operative in all cases in which immobilization of the diaphragm and thorax occurs from any cause, whether it is due to paralysis or paresis of the muscles, to a prolonged faulty posture (as in draining cases) or to voluntary or reflex inhibition as a result of pain or inflammation in the sublying structures. These authors and many others believe this to be the mechanism in the massive pulmonary atelectasis observed as a complication after upper abdominal operations. They point out that the interference with the respiratory movements is a predisposing factor, not only in the formation of mucous plugs in the bronchi, but also in the inability to expel them.

The following two reports illustrate the important clinical features of this type of case.

CASE 3—A middle-aged Italian was admitted to the surgical service of Dr. Bandler at the Post-Graduate Medical School and Hospital with a diagnosis of left pyonephrosis, for which a nephrectomy was performed on March 19, 1929, under general anesthesia. One day after operation, the patient suddenly developed pain in the chest, severe dyspnea, moderate cyanosis and a distressing cough, with high fever. Pneumonia was suspected. He was seen by me six days later, at which time he appeared acutely ill with marked dyspnea and a distressing unproductive cough as the outstanding symptoms. Physical examination of the chest revealed the following significant observations. The right hemithorax appeared shrunken and practically immobile during respiration, while there was prominence and increased mobility of the left. There was marked dullness over the right upper lobe, flatness over the right lower lobes and hyperresonance over the entire left hemithorax. On auscultation, the breath sounds were harsh bronchial to the third rib on the right, weak to absent below that and exaggerated normal over the entire left lung. No râles were elicited. The trachea and heart seemed definitely displaced to the right.

Such physical signs occurring in a patient shortly after an upper abdominal operation at once suggested the probable diagnosis of acute massive pulmonary atelectasis. While such a clinical picture may be produced by pneumonia, pleurisy, spontaneous pneumothorax, pulmonary embolism or infarction or by an acute cardiac accident, the physical signs were characteristic of acute massive pulmonary atelectasis and seemed to justify such a diagnosis. Figure 1 *A* shows the roentgen appearance of the chest at that time. The homogeneous shadow throughout the major portion of the right lung field, the marked displacement of the trachea, heart and diaphragm toward the affected side and the compensatory emphysema in the left lung were interpreted as characteristic of massive pulmonary atelectasis of the major portion of the right lung.

As the patient failed to improve after eight days of expectant treatment, intervention with the bronchoscope had to be resorted to. Bronchoscopic examination by Dr. C. J. Imperatori revealed the bronchi of the middle and lower lobes to be occluded by thick tenacious green mucus about 6 cc of which was aspirated (this showed a pure growth of the green streptococcus on culture). The bronchoscopy

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<sup>8</sup> Elliott and Dingley. Massive Collapse of the Lungs Following Abdominal Operations, *Lancet* **1** 1305, 1914.

was well borne by the patient, and immediately following it he appeared considerably relieved of his dyspnea. At the same time there was evidence of increased aeration in the upper half of the right lung, and numerous moist rales were heard over this area. Roentgen examination of the lungs confirmed the physical signs of improved aeration in the upper part of the right lung.

The next day, although the patient appeared more comfortable, the chest signs were once again those of extensive massive collapse. He was having a distressing cough and was expectorating thick tenacious green mucus with great difficulty. After a second bronchoscopic aspiration on March 29, there was evidence of good aeration throughout the right lung, and this was confirmed by roentgen examination immediately after bronchoscopy. Figure 2 *A* shows marked clearing of the density in the right hemithorax as well as the partial return of the trachea, heart and diaphragm to their normal position. On March 31, the temperature, pulse



Fig 1 (case 3)—*A*, postoperative massive pulmonary atelectasis involving most of the right lung. Note the displacement of the trachea and heart to the affected (right) side. *B*, made shortly before the second bronchoscopy, showing only slightly increased aeration in the right upper and lower lobes.

rate and respirations were normal, and the patient appeared comfortable and free from pulmonary complaints.

This case illustrates the characteristic clinical features of acute massive pulmonary atelectasis following an upper abdominal operation: the sudden onset with acute respiratory symptoms and shock one day post-operatively, the classic physical signs of the condition, the corroborative observations on roentgen examination, the discovery and removal of the occluding tenacious mucous plugs with the aid of the bronchoscope with rapid clearing up of the entire clinical picture. Of interest from the point of view of mechanism is the occurrence of the atelectasis on the side contralateral to the operation, a condition apparently determined in

this case by the persistence of the patient in lying on his right side because of habit as well as because of pain in the operative wound on the left side. That a similar mechanism may be operative in other cases of contralateral collapse is not improbable.

The other case is that of a patient from Dr. Heyd's surgical service.

CASE 4—The patient suddenly developed signs and symptoms of a severe pulmonary complication in the right lower lobe one day after a cholecystectomy. A few days later, he appeared acutely ill, with high fever, marked dyspnea, considerable cyanosis and an annoying productive cough. Physical examination of the lungs revealed evidence of bilateral bronchitis, but in addition, in the right base, there was marked dullness to flatness, the breath sounds were feeble

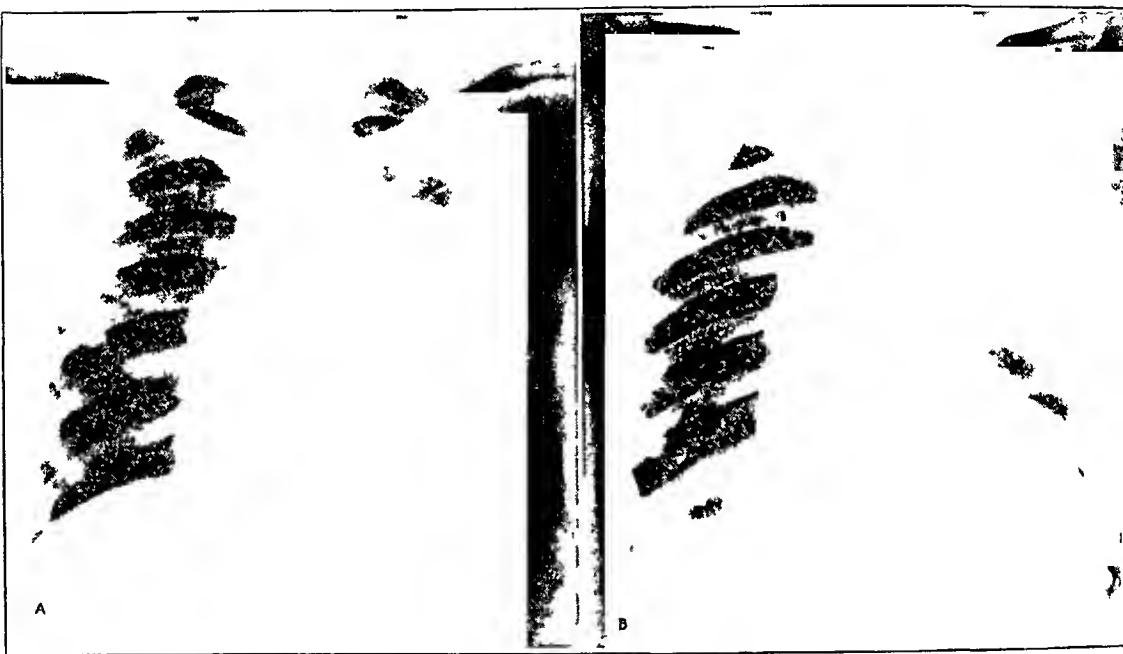


Fig 2 (case 3) —*A*, roentgenogram made immediately after the second bronchoscopic aspiration of the occluding mucus from the bronchi of the right middle and lower lobes. Note the markedly improved aeration of the right lung and the partial return of the mediastinal structures toward their normal position. Patient's pulmonary signs and symptoms greatly improved. *B*, made four days later, showing still further clearing of the right lung. The patient was free from all pulmonary signs and symptoms.

or absent, and few dry expiratory rales were heard. In the absence of signs pointing to a subdiaphragmatic process, the diagnosis to be considered included the following: pneumonia, circumscribed massive atelectasis, pulmonary infarction and pleural effusion. While ordinarily pneumonia would have been considered the most likely diagnosis, circumscribed massive atelectasis was strongly suspected because the condition occurred postoperatively under circumstances which strongly favor its development. Particularly noteworthy in the roentgenogram (fig 3) is the marked elevation of the right side of the diaphragm, a circumstance which suggested that atelectasis was an important factor in the patho-

logic process in the right lower lobe, if indeed, it was not the sole process. The entire clinical picture, as well as the physical signs, seemed to favor this interpretation.

This case illustrates the ease with which circumscribed massive atelectasis may be overlooked or mistaken for other conditions, and also suggests that the frequency with which it is discovered clinically is in proportion to the diligence with which it is looked for.

In brief, the essential mechanism in the production of pulmonary atelectasis in this group of cases is as follows. The primary factor is an interference with the respiratory movements through muscular paresis

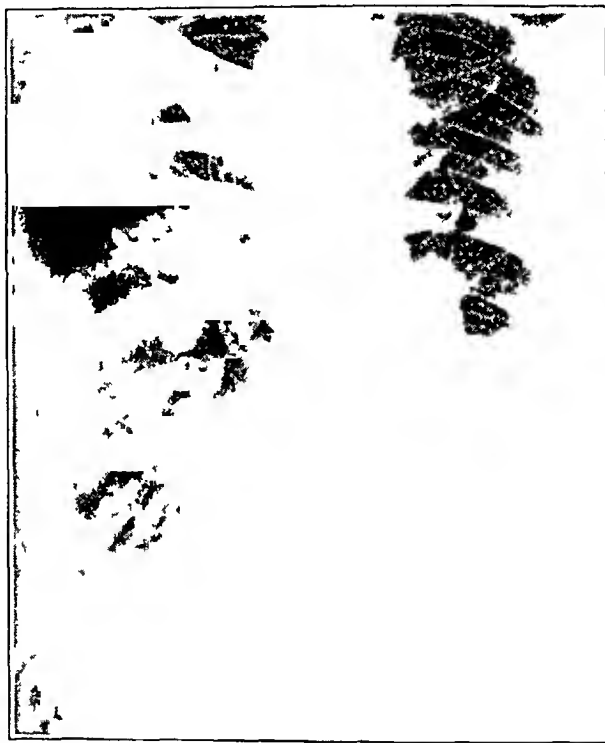


Fig 3 (case 4)—Roentgenogram of the lungs of a patient who suddenly developed signs and symptoms of a severe pulmonary complication in the right lower lobe following cholecystectomy. Note the marked elevation of the right side of the diaphragm which indicates that extensive atelectasis is an important factor in the pathologic process in the right lower side, if it is not the sole process.

or paralysis, voluntary or reflex inhibition of the muscles of respiration from pain or inflammation, prolonged faulty posture, etc. When with this is associated an increase in the bronchial secretions and a suppression of the cough reflex, the accumulated and retained secretions will occlude the bronchi and thus lead to atelectasis.

Lee, Tucker and Clerf<sup>9</sup> recently published an interesting experiment in which the aforementioned mechanism was put to a rigorous test when

<sup>9</sup> Lee, W. E., Tucker, G., and Clerf, L. Post-Operative Pulmonary Atelectasis, *Ann Surg* 88:6 (July) 1928.



they reproduced in the dog the entire clinical picture of postoperative massive collapse. A normal dog was narcotized with morphine and etherized, and then an operative incision was made in the right upper quadrant, entering the abdominal cavity. The wound was carefully closed by sutures, and the upper part of the abdomen was strapped with broad strips of adhesive plaster which encircled the lower portion of the costal arches. The dog was laid and kept on his right side. With the aid of the bronchoscope about 7 cc of secretions previously removed from the bronchus of a patient with a clinical case of pulmonary atelectasis was introduced into the right main bronchus of the dog. The coughing and struggling which ensued resulted in the drawing of the secretion into the deeper portion of the bronchial tree. In order to eliminate the cough reflex, the dog was further narcotized with sodium iso-amyl-ethyl barbituric acid. At the end of three hours all the characteristic physical and roentgen signs of massive pulmonary atelectasis of the right lung were reproduced in this experimental animal.

Jackson and Lee<sup>2</sup> were able to demonstrate the existence of occluding collections of mucus post mortem in two such postoperative cases. They also reported having seen such obstructing masses of mucus in vivo, and when they had removed these with the aid of the bronchoscope, the lung returned promptly to its normal state. From such observations these authors were able to formulate some definite rules for prophylaxis and treatment of this postoperative complication. The prophylactic measures they suggested included the following: the choice of anesthetic agents which are least irritating to the bronchi, and the use of local anesthesia wherever practicable, the conservative use of morphine because of its inhibiting effect on the normal cough reflex, the avoidance of prolonged fixed postures postoperatively. As regards the treatment of the condition, when once established they emphasize the great therapeutic value of bronchoscopic removal of the occluding bronchial secretions in those patients with postoperative massive atelectasis who do not promptly recover spontaneously or with the aid of the simple maneuver suggested by Sante<sup>10</sup> of rolling the patient back and forth on the unaffected side. In experienced hands bronchoscopic aspirations are without danger, are well tolerated even by the sickest patient, and are most effective in promptly relieving the condition thus preventing the possible development of pneumonia in the atelectatic lung.

*The Mechanism of Massive Pulmonary Atelectasis in Cases of Bronchial Stenosis Due to Extrabronchial Pressure*—This relatively small group includes all those cases in which the primary factor is progressive bronchial stenosis due to increasing extrabronchial pressure by

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10 Sante T R Massive Collapse of the Lung J A M A 88 1539 (May 14) 1927

an encroaching neoplasm, aneurysm, mass of bronchial glands or sclerotic process. However, before acute massive pulmonary collapse can take place, a mechanism must be developed which will produce sudden and complete occlusion of the stenosed bronchus.

A number of such reports have recently appeared in the literature. One of the cases of massive pulmonary atelectasis reported by Farris<sup>11</sup> was shown at autopsy to be due to obliteration of the main bronchus by pressure of a large caseous mass.

Wessler and Jaches<sup>12</sup> described an interesting experience in a child 3 months of age who presented paroxysmal attacks of dyspnea and more or less constant stridor. These symptoms were found to be due to the pressure exerted by a mass of tuberculous glands in the upper mediastinum, which apparently produced complete obstruction of the bronchus of the upper lobe and only partial obstruction of the bronchi of the lower lobes. The diagnosis was made from the roentgen appearance of the lungs which illustrated the interesting result of obstructive atelectasis in the upper lobe and obstructive emphysema in the lower lobes occurring in the same lung at the same time. The mechanism involved in such a phenomenon was described earlier in this paper.

Packard<sup>3</sup> reported a case of massive pulmonary atelectasis with a sudden onset and gradual disappearance. The probable explanation of the mechanism in this case as offered by that author is that enlarged tracheobronchial lymph nodes produced stenosis of the bronchus by pressure, which was later relieved by a diminution in the size of the lymphoid mass.

Obviously the same mechanism operates when bronchial compression with stenosis is caused by a mediastinal tumor or aneurysm. Of interest in this connection is the case reported by F. J. Hirschboeck<sup>13</sup> in which at postmortem examination it was found that the massive atelectasis of the left lung was apparently due to bronchial obstruction from compression by an aneurysm in the arch of the aorta and to collections of mucus and pus totally occluding the partially stenosed bronchus. Although in this case the atelectasis occurred after an upper abdominal operation, the foregoing observations are at least suggestive as a probable explanation of the mechanism involved, the bronchial compression by the aneurysm was undoubtedly a powerful predisposing factor, and the importance of retained bronchial secretions in effecting complete occlusion of the bronchus is at least noteworthy.

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11 Farris, H. A. Atelectasis of the Lung, *Canad. M. A. J.* **25**: 808, 1925.

12 Wessler, H., and Jaches, L. *Clinical Roentgenology of Diseases of the Chest*, 1923, p. 49.

13 Hirschboeck, F. J. Massive Collapse of the Lung. With Report of Necropsy, *Minnesota Med.* **11**: 135 (March) 1928.

Massive pulmonary atelectasis may also occur as a complication of chronic pulmonary disease, particularly tuberculosis, when marked peribronchial sclerosis will result in stenosis of the involved bronchi. Packard<sup>3</sup> described the case of a young tuberculous woman in whom massive atelectasis of the left lung occurred with marked suddenness. Postmortem examination of the lung two years later revealed dense fibroid tissue around the main stem bronchus practically obliterating its lumen. In the opinion of the author, the massive atelectasis was the result of this bronchial stenosis. Because of the sudden onset of the massive atelectasis in this case, it is only fair to assume that something must have happened immediately before the catastrophe to render the bronchial occlusion complete. Whether the final mechanism leading to complete occlusion was one of bronchial spasm of vasomotor origin, or whether it was due to mucosal tuigescence with retained secretions, one can merely speculate.

Of especial interest in this connection is the following report of a case which was under observation for a number of years.

CASE 5—Mrs. Y. Z. first came under my care in November, 1922, when at the age of 28 she was admitted to a tuberculosis sanatorium with a diagnosis of pulmonary tuberculosis based on few symptoms, insignificant physical signs but roentgen evidence of a fibrotic lesion in the apex of the left lung. After eight months at the sanatorium, she was discharged with a diagnosis of inactive minimal pulmonary tuberculosis complicated by seasonal asthma, of which she had shown moderate symptoms during the months from May to July.

In the spring of 1924, and again in 1925, the patient received injections of pollen (orchard grass) with symptomatic relief from the seasonal asthma. In the meantime, she has continued to do fairly well, showing no significant changes in the physical and roentgen signs in the chest. Figure 4 *A* is the photograph of a film made in December, 1924, and it merely shows evidence of a fibrotic lesion in the apex of the left lung.

In January 1926, there was a moderate increase in cough and expectoration. Physical examination of the chest disclosed a few coarse râles in the left upper lobe, and roentgen examination at this time revealed evidence of somewhat increased fibrosis there.

On April 10, 1926, the patient was examined by me at my office and showed no further change in the physical and roentgen signs. During that examination, skin tests were made. While the patient was waiting for the results of the skin tests to be read, she was suddenly seized with a severe spell of coughing. Marked dyspnea developed rapidly, and the patient appeared to be experiencing a severe attack of asthma. Moderate cyanosis soon developed, and prostration increased rapidly.

Physical examination of the chest at this time revealed the following significant observations: relative immobility of the upper part of the left hemithorax, marked dulness, bronchocavernous breathing and no râles over the left lobe, marked displacement of the trachea to the left, and apparent displacement of the heart to the left. In the right lung, and to a lesser extent in the left base, wheezing respirations suggestive of asthma were heard.

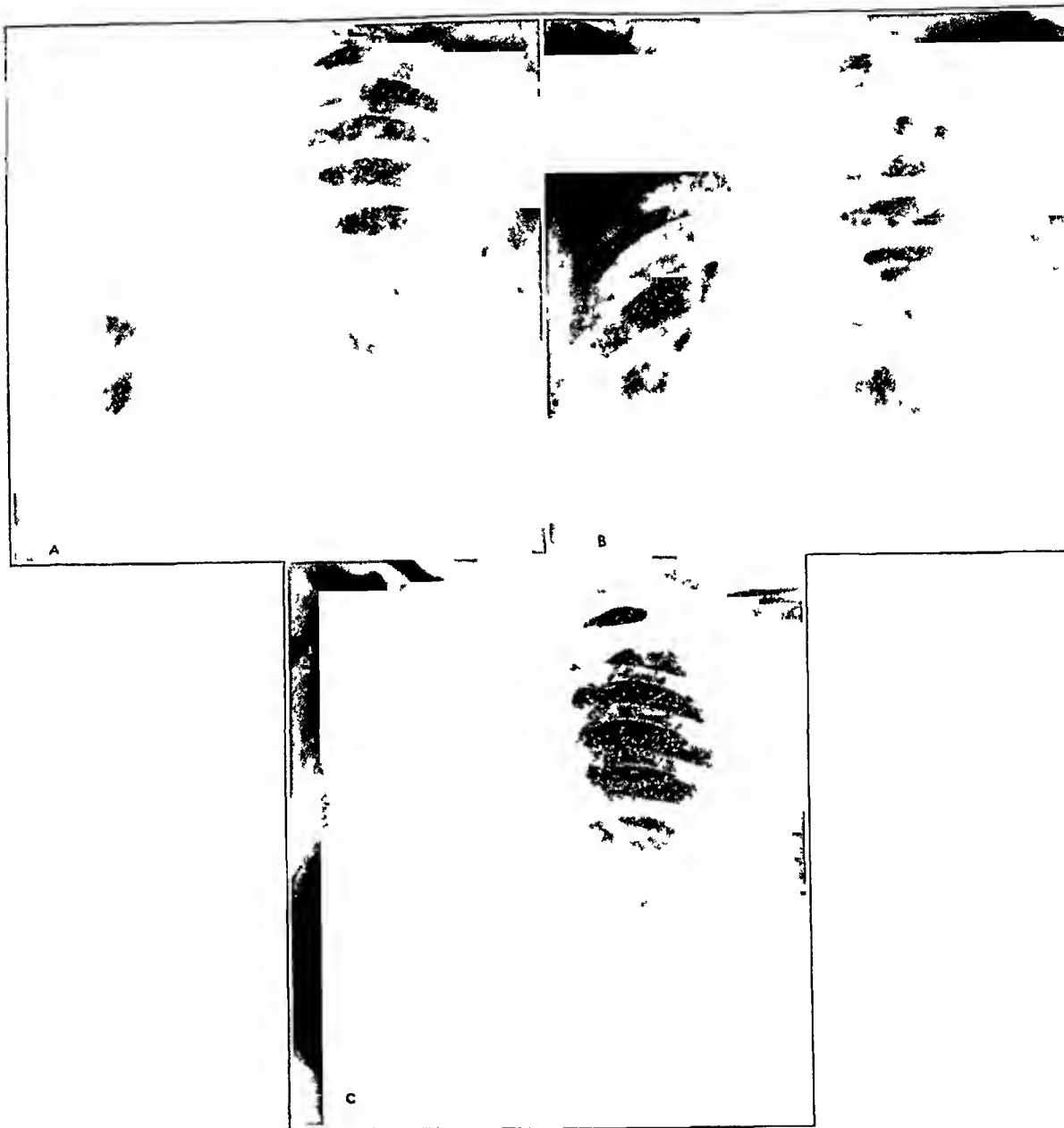


Fig 4 (case 5) — *A*, roentgenogram made in December, 1924, showing infiltration with fibrosis involving the upper portion of the left upper lobe. Note the normal position of the trachea and mediastinum. This roentgenogram represents approximately the pulmonary status of the patient from 1922 to April, 1926. *B*, made on April 10, 1926, one hour after the sudden onset of acute respiratory symptoms. Note the partial atelectasis of the left upper lobe with resulting marked displacement of the trachea to the left as well as the less marked displacement of the heart. Also note the compensatory emphysema in the uncollapsed parts of the left lung. This picture of the lungs remained unchanged during the next two and three-fourths years. *C*, made in March, 1929, two weeks after sudden onset of acute respiratory symptoms. The appearance is characteristic of massive atelectasis involving the major portion of the left lung. Bronchoscopic examination revealed stenosis of the bronchi of the left lung probably due to marked peribronchial sclerosis with retained mucus secretions in them.

This sudden change in physical signs was puzzling at first, but its probable significance was evident after a study of the roentgenogram made at the time (fig 4 B), which showed evidence of circumscribed atelectasis in the left upper lobe. The increased density of the shadow in the upper lobe, as well as the sudden and marked displacement of the upper mediastinum to the left, were particularly impressive in that connection.

After several weeks of illness with dyspnea, cough and moderate fever, the patient began to improve rapidly. At the end of two months, and until February, 1929, she was well enough to attend to her household duties, slight dyspnea and cough being the only residual symptoms. During all this time the physical and roentgen signs remained unchanged and were those just detailed.

About the middle of February, 1929, following an infection of the upper respiratory tract, the patient's cough became more severe, and the expectoration was scanty, tenacious and difficult to raise. Four days later, she experienced a sudden attack of marked dyspnea and pain in the left side of the chest. The dyspnea subsided spontaneously after a while, but it would recur on the least exertion, particularly at night. At the same time the temperature began to rise, reaching 102 F at night. When I saw the patient six days later, she presented the classic signs of massive pulmonary atelectasis involving the major portion of the left lung. The signs were so characteristic of the condition that the other diagnostic possibilities which had to be considered, such as pneumonia, pleurisy with effusion, thick pleura, etc., were soon discarded as improbable.

At this time the patient was admitted to the medical department of the New York Post-Graduate Hospital. After the roentgen examination (fig 4 C) confirmed the diagnosis of massive atelectasis, a bronchoscopic examination was made by Dr. Imperatori in order to determine the cause of the atelectasis. The following possibilities were originally considered: (1) bronchial stenosis due to peribronchial fibrosis, (2) benign endobronchial tumor (benign because of the long course), (3) foreign body in the bronchi and (4) bronchial compression due to mass of glands or other mediastinal tumor (soon ruled out by the result of the roentgen examination). The purpose of the bronchoscopy was not only to establish the etiologic factor, but also to attempt to remove it if possible: by extraction if due to foreign body, by excision if due to benign neoplasm, by aspiration, if due to removable plugs of mucus.

The bronchoscopic examination revealed the existence of marked stenosis of the main stem left bronchus as well as occluding secretions which were aspirated. Following the bronchoscopy, the patient's breathing was much improved, and she began to expectorate large amounts of sputum. A roentgenogram made immediately after the bronchoscopy showed increased aeration in the left upper lobe. However, as neither the symptomatic relief nor the improved aeration in the upper lobe lasted more than twenty-four hours, the patient was subjected to another bronchoscopic examination seven days later. At this time a smaller bronchoscope was used, and an attempt was made to enter the smaller bronchial radicles, but these were found totally stenosed. Although aspiration of the mucus was attempted, the patient did not again experience symptomatic relief.

Bronchoscopic aspirations of the locked-in secretions having proved ineffectual, the other therapeutic measures to be considered included pneumothorax and the usual expectant hygienic-dietetic regimen. In this type of case the object of pneumothorax therapy is not to collapse the lung further but to restore a more or less normal intrathoracic equilibrium by allowing the mediastinal structures to return to their central position in the thorax. This plan of therapy might still be resorted to if the expectant hygienic-dietetic treatment should prove ineffectual.

Here is a case of a tuberculous person with a manifest tendency to marked peribronchial fibrosis and a disposition to attacks of spasmodic asthma in whom acute massive atelectasis of the left upper lobe was followed nearly three years later by a similar collapse of the lower lobe, in whom bronchoscopic examination revealed marked bronchostenosis as well as occluding secretions of mucus as the obvious cause of the condition, and who, following the bronchoscopic aspiration of the bronchial mucus, showed temporary symptomatic improvement as well as increased aeration in the right upper lobe only to relapse to a state of complete atelectasis twenty-four hours later. From these circumstances it seems fair to infer that the mechanism of the massive atelectasis in this case was as follows. The essential primary factor was progressive bronchial stenosis due to increasing peribronchial fibrosis, however, the secondary mechanism, which was responsible for the sudden and complete occlusion of the stenosed bronchus thus precipitating the massive pulmonary atelectasis, was probably that of bronchial spasm and retained mucus secretions. In the presence of a tendency to fibrosis, the temporary complete occlusion by spasm and retained mucus was soon rendered permanent by the still more increased fibrotic changes which rapidly followed the development of atelectasis.

While in this discussion of the subject the greater emphasis has been placed on the elucidation of the mechanism involved, its clinical features have been emphasized sufficiently to show its importance from the point of view of diagnosis, differential diagnosis, prophylaxis and treatment.

#### SUMMARY AND CONCLUSION

1 Massive pulmonary collapse or atelectasis has been described in a great variety of clinical conditions. However, careful analysis of this vast clinical material will disclose that most of the cases can be classified into three groups.

Group 1 Cases with gross or manifest bronchial obstruction by foreign body, endobronchial neoplasm, retained blood clots, diphtheritic membrane, etc.

Group 2 Cases in which the primary factor is an interference with the respiratory movements, through muscular paresis or paralysis, voluntary or reflex inhibition of the muscles of respiration from pain or inflammation, prolonged faulty posture, etc. When with this is associated an increase in the bronchial secretions and a suppression of the cough reflex, the accumulated and retained secretions will occlude the bronchi and thus lead to atelectasis.

Group 3 Cases in which extrabronchial pressure due to neoplasm or aneurysm enlarged glands or sclerotic tissue leads to gradual stenosis of the bronchus the bronchial occlusion being rendered complete either by mucosal tuilage or by bronchial spasm, with retained secretions.

In all these cases, following the bronchial occlusion, the alveolar air is absorbed by the pulmonary circulation and atelectasis results

2 Cases are presented to illustrate the essential mechanism in these three main groups

3 The clinical picture as well as the physical and roentgen signs are characteristic, and they are similar in all cases. The onset is usually sudden, with evidence of marked respiratory embarrassment and shock. The characteristic physical signs are markedly diminished mobility of the involved hemithorax, narrowing of the interspaces, pulling in of the trachea, heart and diaphragm toward the affected lung, flatness to percussion, harsh or absent breath sounds, and no râles over the affected lung. The roentgen examination reveals a dense homogeneous shadow where the atelectasis exists, and is corroborative of the displacement of the trachea, heart and diaphragm toward the affected lung.

4 This clinical picture and some of the physical signs may simulate pneumonia, pleurisy with effusion, acute cardiac accident (dilatation, coronary occlusion, etc.). The diagnosis of the condition is not difficult if the atelectasis is extensive, if partial only, its recognition is not easy.

5 It should always be thought of in the examination of patients with pulmonary complications in diphtheria and following upper abdominal operation or tracheotomy.

6 In cases of massive pulmonary atelectasis with no obvious cause, the possible obstruction of the bronchus by a nonopaque foreign body or by an endobronchial neoplasm should be investigated by a bronchoscopic examination. If the examination reveals no endobronchial obstruction, but the existence of a complete or partial stenosis, compression of the bronchus by neoplasm, enlarged glands, aneurysm or peribronchial fibrosis should be suspected.

7 Early recognition of the condition is important, because in many cases its treatment at that time is simple and successful. In postoperative massive atelectasis the simple maneuver of rolling the patient on his unaffected side is usually effective. In late postoperative cases and in all cases of foreign bodies, bronchoscopic aspiration or extraction of the occluding substance is most effective in relieving the condition and preventing complicating pneumonia.

8 Pulmonary atelectasis of the more circumscribed variety is also of great clinical significance. It is of frequent occurrence as a postoperative complication, and it is an important factor in pulmonary pathologic processes associated with extensive fibrosis and with pulmonary neoplasm. Its recognition and proper evaluation will solve many puzzling situations in the study of pulmonary cases.

## Book Reviews

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MORPHOLOGIC VARIATION AND THE RATE OF GROWTH OF BACTERIA By  
ARTHUR T. HENRICI, M.D. Volume 1 Price, \$3.50 Springfield, Ill.  
Charles C. Thomas, 1928

This monograph, the first of a series to be written on microbiology, represents in its substance the author's own work on the subject. Chapter 1 deals with the problem of the morphologic variation of bacteria. Several of the more recently advanced hypotheses on the nature and growth of bacteria are presented at some length. In discussing them the author criticizes particularly the assumption of these investigators that bacteria go through life cycles because the available data are far too few and incomplete to warrant such conclusions. He then indicates the purpose of his work, namely, to make continuous quantitative observations on individuals and populations of bacteria under closely controlled conditions during all the phases of their growth.

After stating the technique in considerable detail he proceeds to the study of several micro-organisms, *Bacillus megatherium*, the colon bacillus, the diphtheroid bacillus, and the cholera vibrio. Definite characteristic changes in the size and shape of the individual bacteria were found at different periods of growth which were constant for the several variations of micro-organisms studied. The rates of growth of cell populations were also measured and found to follow regular curves. The great number of data obtained are represented in drawings and graphs in such a way as to give a much more complete picture of the morphologic changes occurring during the life of these types of bacterial cells than has heretofore been possible.

In a final chapter entitled "On Cytomorphosis in Bacteria" the author brings together evidence for considering the changes occurring in cultures of bacteria as analogous to the sequential alterations exhibited by the cells of multicellular organisms and termed by Minot "cytomorphosis."

At the end of the book is a series of tables giving the actual experimental data from which the charts and graphs are made. The bibliography and index of both authors and subjects follow.

The work constitutes a valuable contribution to the knowledge of bacterial growth and sets a high standard for the other volumes of this series that are to follow.

DIE KRANKHEITEN DES HERZENS UND DER GEFÄSSE By DR. ERNST EDENS  
Paper Price, 66 marks Pp. 1057, with 239 illustrations Berlin Julius  
Springer, 1929

In his discussions of various topics Edens follows rather closely the traditional lines of etiology, pathology, diagnosis and treatment. All of the ordinary and many of the rarer diseases will be found included. The comparatively later knowledge revealed largely by the aid of the roentgen ray and the electrocardiograph is fairly presented. There are many helpful illustrations of roentgenograms and electrocardiograms. We are glad to see that valvular diseases are still regarded as worthy of full discussion. In some recent works they have been deemed of such minor importance as compared to myocardial diseases and irregularities as to be accorded scanty consideration.

Two features are worthy of special comment. The treatment for weakness of the circulatory organs occupies 100 pages, more than 13 per cent of the text, 30 pages being devoted to digitalis alone. This is a larger proportion than is commonly assigned to this one topic. Some condensation with elimination of minor details as to baths, climate, massage, diet and a number of drugs might be advisable.



Many practitioners, however, will probably disagree and will find in these minutiae as to treatment that which will make the book of especial value to them. The other item is the massive bibliography. The index of titles covers 250 closely printed pages. The subdivision of the bibliography into heads corresponding to the chapters makes the book a ready reference work for one who wishes to go to original sources.

One may say that the volume is a comprehensive, reliable and up to date work.

LE PROBLEME DE LA SENSIBILITE VISCERALE ET L'ANESTHESIE DES SPLANCHNALGIES. PAR A. LEMAIRE, Professeur de Clinique Medicale a l'Universite de Louvain. Collection de monographies medicales publiee par la Societe scientifique de Bruxelles. No 3. Pp 80. Paris. Presses Universitaires de France, 1928.

In this monograph of eighty pages, the authors begin with an analysis of the earlier theories of visceral sensibility, those of Lenander, Ross and McKenzie, with their various modifications, and discuss their applicability both in the normal and in the pathologic state. The sensitiveness of the viscera and the adequate stimuli required for the production of pain in the parenchyma, the mucosa, the splanchnic musculature, the serous surfaces and the ligaments are carefully and extensively considered in the first chapter. The authors have made an especial study of the effect of subcutaneous anesthesia on visceral pain, the results are described in the second chapter, in which the old as well as more recent theories, those of Edinger and Verger, are reexamined in the light of these observations. The third and final chapter consists of a brief discussion of the possible ways in which the impulses of visceral sensibility may ascend to consciousness.

The purpose of the monograph is not to present the subject of visceral pain as a settled question but rather to gather all of the theories and facts, including those derived from a long experience with subcutaneous anesthesia and pain of visceral origin, and to determine the extent to which the facts confirm or contradict the theories. The standpoint is conservative, the deductions are carefully made and the attitude is scientific and scholarly. The work should stimulate further research in this field and thereby fulfil one of the chief aims for which it is published.

PROGRESSIVE RELAXATION. A PHYSIOLOGICAL AND CLINICAL INVESTIGATION OF MUSCULAR STATES AND THEIR SIGNIFICANCE IN PSYCHOLOGY AND MEDICAL PRACTICE. By EDMUND JACOBSON, A.M., Ph.D., M.D. Pp 429. Price, \$5. Chicago. University of Chicago Press, 1929.

This book is the result of twenty years of research work in the physiologic and psychologic laboratories of the University of Chicago as well as of clinical experiments and observations in private practice. The author has made extensive studies of muscular action and relaxation and the effect of emotions on them. The chapters on spastic esophagus, mucous colitis, and on the methods of teaching relaxation to nervous patients will be of particular interest to clinicians. The idea of treating nervous states mainly by the induction of muscular relaxation may seem startling. It is another case in which a vicious circle may be broken at an unusual place. It reminds the reviewer of the celebrated cynical utterance of Pascal: "Il faut s'abêtir," meaning that if people use holy water, cross themselves and go through the emotions of worship the spiritual effect comes of itself. In the same way, as mental poise and contentment are associated with a feeling of relaxation so the induction of relaxation may in itself cause a tense and anxious patient to deceive himself into believing that he is at ease mentally. Having had a taste of this comfortable feeling he may persuade himself that he might himself prolong it by not resuming his worries. It is not reasonable to suppose that this method alone will succeed in many cases but it is a rational accessory to other psychotherapeutic procedures.

THE INTERNATIONAL MEDICAL ANNUAL A YEAR BOOK OF TREATMENT AND PRACTITIONER'S INDEX Price, \$6 New York William Wood & Company, 1929

This annual lives up to its reputation for giving a most careful review and thoughtful digest of recent medical literature. Compiled in the form of a dictionary, the material presented is too diverse to be criticized in detail. Mention should be made of the many helpful suggestions regarding therapy. For example it is pointed out that the diuretic action of epinephrine in asthma may be prolonged by massaging the site of injection. Diagnostic procedures, such as cholecystography and renal function tests, are discussed at length. For the surgeon one finds described a new upper abdominal incision which has been useful in avoiding incisional hernia. The articles on obstetrics include a note on a method of extracting the adherent placenta without putting the hand into the uterus. In every field one finds suggestions of practical value. One may not always agree with the opinion of the individual author, but the material is presented in such a way that one may draw his own conclusions. Some omissions will be noted. In discussing the injection treatment of varicose ulcers no mention is made of the use of 50 per cent dextrose solution which by some is considered the substance of choice. Such defects, however, are too few to detract from the general usefulness of the volume which should prove a worthwhile addition to the library of the practitioner for whom it is primarily intended.

UNTERSUCHUNGEN UEBER PORPHYRIE MIT BESONDERER BERUECKSICHTIGUNG DER PORPHYRIA CONGENITA By MAX BORST AND HANS KONIGSDORFFER, JR Price, 38 marks Leipzig S Hirzel, 1929

The book is based on a study of a case of congenital porphyry in a man who died at the age of 32. His condition had been investigated clinically and biochemically in great detail and had previously been reported by Fischer, Gunther and Weiss. Borst reports the gross and microscopic observations of the autopsy. Grossly, there was porphyrin discoloration or "hemosiderosis" of the skin and the entire skeleton, spleen, liver, lymph nodes, pancreas and kidneys, and histologically of practically all of the tissues of the body. Microhistochemical and physical analyses of the pigments in the various organs and tissues were made by Fischer. Konigsdorffer studied the fate of porphyrins administered experimentally to animals. They came to the conclusion that porphyry is a constitutional anomaly. There is not an incomplete synthesis of hemoglobin, myoglobulin and histohematin or cytochrome as has been claimed. They believe that in congenital porphyry there is an arrestment of the metabolism of porphyrin at an intermediary stage, giving the abnormal pigments met with in the condition. Porphyrin is synthesized in the red blood corpuscles. An extensive review of the literature on the subject is also given.

CLINICAL ELECTROCARDIOGRAMS THEIR INTERPRETATION AND SIGNIFICANCE By FREDERICK A WILLIUS, M.D, Section on Cardiology, the Mayo Clinic, Rochester, Minn, and Associate Professor of Medicine, the Mayo Foundation, University of Minnesota Cloth Price, \$8 Pp 219, with 368 illustrations Philadelphia and London W B Saunders Company, 1929

This book consists, for the most part, of electrocardiograms taken from the author's collection. The author's interpretation of each tracing is given together with clinical diagnosis of heart disease in the patient from whom the tracing was made. The clinical significance of the tracing is discussed in many cases, and a few tables are included to indicate the possibility of a prognostic value in certain abnormal characteristics of the electrocardiogram.


The book is well prepared. The tracings are clearcut and well marked, and the explanatory remarks are clear and concise.

As far as the subject matter is concerned with the exception of the author's observations on the prognostic significance of certain aberrations of the T wave, nothing is contained in the book that has not been said before. The interpretation of the tracings is, for the most part, clear and convincing, but interpretations and statements occur which might be open to argument. To mention a few, in the section on auricular flutter, the interpretation of some of the tracings is rather doubtful. Also, it is difficult to correlate the coincidental occurrence of auricular flutter and sino-auricular block.

The statement that "occasionally the ventricular action in auricular fibrillation is rhythmic, especially with slow rates" will surely be challenged.

Many of the tracings depicting paroxysmal ventricular tachycardia do not fulfil the requirements accepted as necessary for that diagnosis.

The author expresses in his preface the hope "that the illustrative examples may aid those whose experience in this field (electrocardiography) is limited." One gets the impression that the book is rather advanced for this purpose and contains much discussion of a speculative nature. Such discussion might prove confusing and misleading to the inexperienced. The greatest value of the book lies in the variety of the tracings. Almost every variety of electrocardiogram, normal and abnormal, may be found and is clearly described. There is, in addition, an excellent bibliography.



## CONSTITUTIONAL VARIATION AND SUSCEPTIBILITY TO DISEASE<sup>\*</sup>

WADE H. BROWN, M.D.  
NEW YORK

The conception of disease as a product of a constitution is a heritage from antiquity, based on observation and experience<sup>1</sup>. As is well known, the term constitution was originally used in a broad sense to denote a fixed or a prevailing state or condition. It was applied primarily to climatic and meteorological conditions, but was also used with reference to disease and to man.

To the ancient Greek, disease was a product of the interaction between man and his environment, still, environment was given first place, much as it is today, but for a different reason. The Greek regarded both man and disease as products of environment, while in recent years investigators have been inclined to disregard man and to stress the importance of a single environmental factor. This change of views is attributable to modern bacteriology. After centuries of abstract speculation concerning the cause of disease, bacteriology came like a beam of light into the darkness, micro-organisms were realities and offered the first hope of the solution of the problems of disease by the use of scientific methods. Bacteriology and immunology were like new toys. For the time being, man and his environment were cast aside and attention was focused on the so-called causative agents of disease and on the reactions produced by them when introduced into the body. New conceptions of disease were evolved with man and the micro-organism as the central figures. Subconsciously, the old idea of disease as a product of the interaction between man and his environment was first supplanted by the idea of an interaction between man and an infecting organism. Eventually, this simplification was carried

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<sup>\*</sup> Submitted for publication, July 9, 1929.

<sup>1</sup> Read at a meeting of the Harvey Society of New York, Feb. 21, 1929.

<sup>†</sup> From the Laboratories of the Rockefeller Institute for Medical Research.

1. The ancient conception of the relation between man and his environment is clearly set forth in the Hippocratic treatise on "Airs, Waters, and Places" which is one of the most remarkable medical documents of all times. It contains many of the fundamental ideas of the modern conception of human constitution and climatology, including the factors of heredity and the beneficial effects of sunshine. It is also remarkable for the accuracy of the observations made when viewed in the light of results of present day experiments. In this connection, it will be noted that the results of many of the experiments referred to in this paper are neither more nor less than confirmations of Hippocratic teachings translated into modern terminology.

still further. The causative agent of disease became the important factor, while man was assigned the role of the victim, or object, rather than the subject of disease. In this new form, the idea of interaction between host and infecting organisms was verbally retained, but it was given scant consideration in explaining phenomena of disease, except when some specific reaction was concerned. In processes of reasoning, the micro-organism became endowed with many potentialities, both real and imaginary, while the host came to be regarded in somewhat the same light as a standard culture medium. Any deviation from the usual or expected course of events was attributed to some change affecting the micro-organism, it rarely occurred to any one that the condition presented might be attributable to the host, and even if it did, there was no means of explaining the observed facts. So it came to be considered that a man was just a man and an animal just an animal, fixed and immutable, but a micro-organism was a being endowed with infinite potentialities.

A paradoxical situation was thus created. The importance of such factors as age, sex, family, race and even individual predisposition was clearly recognized, so were the factors of climate, season and weather, but these factors were still abstract conceptions and could not be fitted into a scheme of things founded on the results of carefully controlled experiments which dealt with micro-organisms and defensive or immunologic reactions. It was inevitable, therefore, that explanations of phenomena of disease should depend more and more on the body of accumulated facts concerning micro-organisms and that less consideration should be given to factors which were not understood or which represented vague and intangible quantities.

Apparently, the pendulum has completed its swing in this direction. There is a reawakening of interest in the host and his environment, with a growing realization of the fact that in infectious diseases there are two systems of variables, and that one cannot hope for a satisfactory solution of the problems so long as one arbitrarily treats either system as a constant and attributes all variations in results to the other. The problem which now confronts one is to define the potentialities of both systems in terms that can be clearly understood. Until this has been done, the analysis of phenomena of infection and disease will be attended with considerable uncertainty.

The study of constitution is only one phase of this great problem, but during recent years much has been done to clarify the relation of man to disease. This is particularly true of the work that has been done in genetics, endocrinology, dietetics, biophysics and the field of epidemiology itself. Finally, under the leadership of Diaper, a notable effort has been made to adapt the precise methods of anthropology to medical requirements and to apply these methods to clinical medicine.

Still, it is extremely difficult to define the constitutional factor in language which conveys a definite meaning or to say how or why one person differs from another, with respect to the general property of susceptibility to disease, or why this property should appear to vary from time to time in a given individual or in a population as a whole. Simple observation and experience tell one that these things are true. No medical tradition is more firmly rooted in the minds of all peoples than this. Moreover, these conditions are applicable to animals as well as to man, one sees them continually in experimental work. They cannot be denied or ignored. They must be explained as simply and directly as possible, and I have taken this for my task, with a full realization of the fact that any explanation that may be offered at this time must be incomplete and is subject to amplification, modification or complete abandonment, as future developments may demand.

#### THE PROBLEM OF CONSTITUTION

There are two firmly established aspects of the problem of constitution, namely, heredity and environment. From the point of view of the bearing of constitution on susceptibility to disease one has to consider the question of factorial potentialities on the one hand, and the functional expression of these potentialities on the other. For the most part, interest in constitution has been centered in problems of heredity and in the study of normal and abnormal constitutional types. For obvious reasons, less attention has been paid to conditions presented by the rank and file of mankind, but it is this phase of the subject in which I am especially interested, as it seems to me that a knowledge of the fundamental principles of constitutional organization and reaction is a prerequisite to the study of any class of persons or of the relation of man to disease. So far, I have been concerned primarily with the study of existing states—physical, chemical and functional—and with the influence exerted by environment on the constitutional status and its functional expression as determined by variations in the reaction to disease.

The conception of the relation between constitution and susceptibility to be presented is merely an outline of certain phases of a complex problem. It is based on experiments which have been in progress for about ten years, and represents the combined efforts of Dr L. Pearce, Dr C. M. Van Allen, Miss Marion Howard, Dr A. R. Harnes, Dr A. E. Casey and me. A great deal of the material to be used has been published, but unfortunately much of it is still in the process of digestion and assimilation. I shall, however, confine myself to facts which have been amply demonstrated.

The problem of constitution turns, first of all, on the determination of what is normal. The usual treatment of this subject is unsatisfactory

The current method of dealing with normality is the method of standardization—the establishment of mean values with limits of variation or of other standards of measurement and the separation of persons into two classes, the normal and the abnormal. It is apparently assumed either that what happens within the limits of normal is of no consequence or that the methods available for drawing distinctions are inadequate. The territory marked off by the upper and lower limits of normal has been entered with the intention of finding out whether normal is just normal or whether something more can be said. A common laboratory animal, the rabbit, has been used, which could be taken apart and, theoretically, reassembled at will, and could be used in an attempt to correlate states of normality with susceptibility to disease, or in studies of the influence of heredity, as well as for collateral studies of constitutional effects produced by disease and effects of constitutional modification on disease itself, whether produced by mechanical, chemical or physical means. In general, this is the field which our studies have covered.

As an approach to the discussion of the problem, one may consider the animal organism to be divisible into three parts: (1) a skeletal and muscular system which is concerned primarily with the performance of mechanical functions or with doing the physical work of the body, (2) a system of organs which carry on and regulate vital processes and support the muscular and skeletal systems, as it were, and (3) the blood and lymph which form a medium of communication and exchange between all parts of the body and, in addition, have particular functions of their own to perform. For present purposes, however, it is not necessary to consider the function of any organ.

It is a well recognized fact that all animals of a given species are constructed in accordance with a common plan and with some regard to quantitative relations between the various parts of the body. Normal functional activity is dependent on the maintenance of these relations within certain prescribed limits, but the limits are sufficiently wide to permit of variation, which is the basis of individuality.

While everyone is aware of the fact that persons differ from one another in respect to the size or weights of organs or parts of the body, just as they do in appearance or other physical characters, there are probably few who have attempted to reduce the question of organic individuality to the basis of a measurable difference. I shall begin, therefore, by assembling organs for three hypothetical animals, using maximum, minimum and mean values per unit of body weight for representative organs as determined by actual observations on a group of 645 normal rabbits. When presented graphically (chart 1) the difference is striking.

Of course, no such animals as these exist nor is it likely that persons of the extreme types could exist. Still, there are animals which differ in one or more of these respects by amounts equal to those

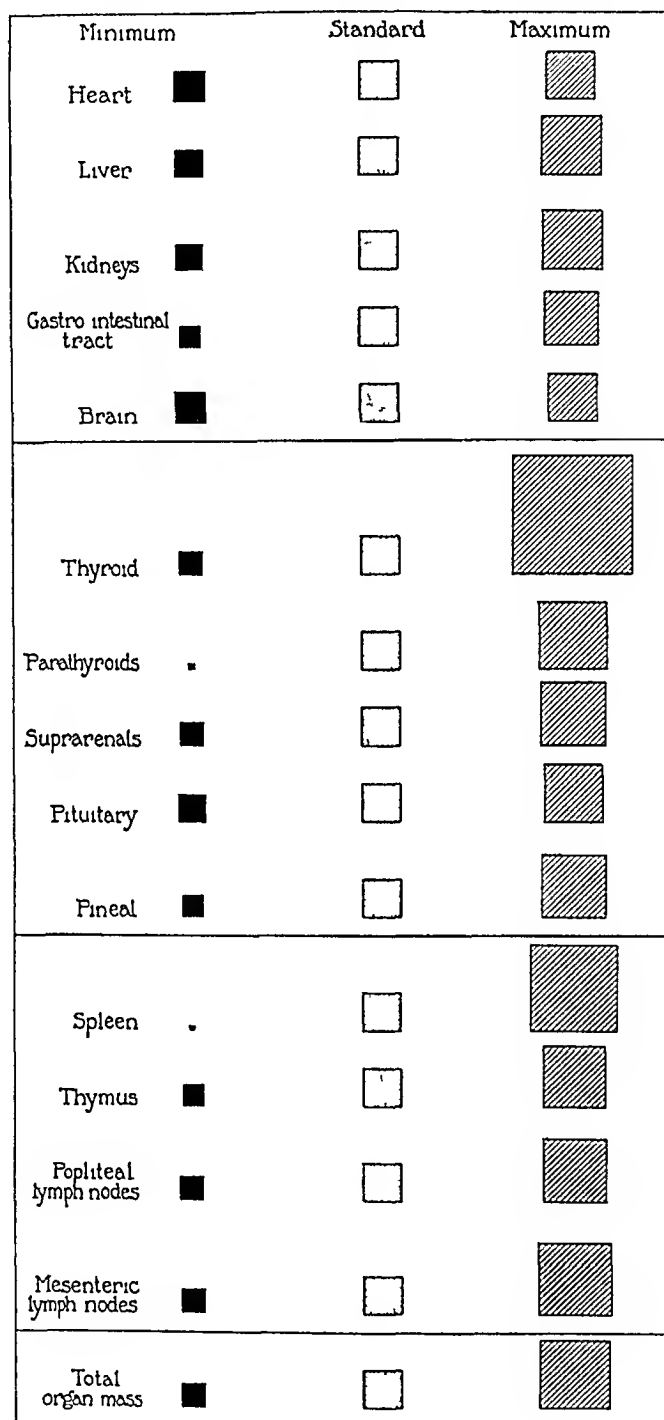


Chart 1—Theoretical range of variation in organic constitution of normal animals. Weights per unit of body weight

indicated in this diagram. A four or five-fold difference in the weight of an endocrine gland or of a lymphoid organ or a twofold difference in the weights of parenchymatous organs, per unit of body weight, is



by no means uncommon, while variations of from 25 to 100 per cent are common. The smaller variations are of the order of the differences in weight or in stature of adult men but in some instances the extremes exceed the difference between dwarf and giant.

These differences in organic constitution are not hypothetical but real, and they raise a second point of fundamental importance, namely, the relation between the weight of an organ, or an assemblage of organs, and the weight of the body which they serve. Within certain limits, the actual weight of most organs and, therefore, the combined mass of all organs, varies directly with the weight of the body, but the exact relations are such as to produce a decided difference in the constitution of large and small animals. There is a tradition to the effect that, in general, large, robust persons are frequently more sus-

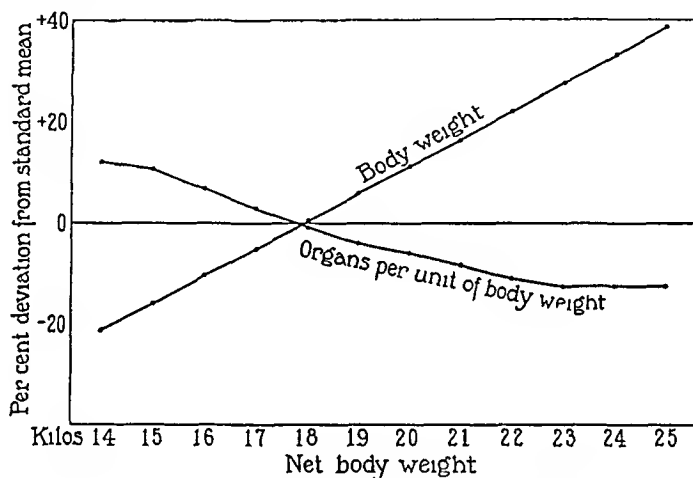


Chart 2—Organ-body weight relation for animals of different weight groups

ceptible to disease than those of the small, wiry type, and that in illness the prognosis is less favorable. This may or may not be true, but there is a constitutional parallel which might warrant such an expectation. The fact is that the mass of organs in proportion to the weight of the body served is distinctly greater for small than for large persons (chart 2). By weighing the results for all organs so as to give them equal value irrespective of size, it is found that, despite the fact that the actual weight of organs increases with the weight of the body, the weight per unit of body weight actually diminishes. Hence, the normal load carried by the organs of small persons may be less and the reserve greater. Applied to the maximum and minimum animals, this means that the constitution of the smaller person approaches the maximum type, while that of the larger assumes the direction of the minimum type. From our material, it cannot be determined with certainty whether this relation is due primarily to breed, age or weight,

independent of these factors, as the condition appears to be one which is influenced by all the factors mentioned

At any rate, it will be seen that the relation of organ mass to body weight, individually and collectively, is one of the basic principles of organic constitution and is applicable to breeds or races, families, sexes, age groups and individuals

As is well known, physical characters such as weight and height are distributed in accordance with the laws of normal or chance distribution. The same is true for the weights of organs and, hence, for organic constitution, that is, in an animal population there is a constant and approximately equal number of animals whose organ mass, in proportion to body weight, is above or below the mean or mode, but in reality most of the curves are skewed or tend to be extended somewhat into the upper ranges, as is the case with measurements of height and body weight. As a simple working formula, it may be said, however, that small, intermediate and large organs will be encountered in the ratio of 1 : 3 : 1. The significance of these proportions will appear later.

Individual differences of organic constitution may be regarded as inherent qualities in that they are probably determined in accordance with the principles of genetic inheritance. They represent potentialities, however, rather than fixed qualities. So far as I have been able to determine, no organic relation or status is absolutely fixed. It is well known that organs change with age and that some, at least, show periodic variations of a seasonal character or in association with some change in physiologic status, such as pregnancy. There is, however, no clearly defined idea of what these variations represent from the point of view of their collective effect on constitution, broadly considered. This situation has, to some extent, been clarified.

I have data on the variations in weight of seventeen representative organs covering a period of three and one-half years. If the results for the entire period are condensed to the basis of a single year, one may obtain an idea of the extent to which different organs vary per unit of body weight and the trend of the variation from month to month (charts 3, 4 and 5). In the first place, one finds that, strictly speaking, not one of the organs studied maintained a constant relation with the body. Even the heart, the kidneys and the brain showed slight but definite variations, of course, the endocrine and lymphoid organs showed the greatest variations.

Without attempting a detailed analysis of the trends of curves, it will be seen that, in a general way, they partake of a seasonal character with distinct differences in the time and direction of the variations. In some instances, there were four clearly defined fluctuations during the year. The thyroid presents a curve of this type with an increase in winter and early spring, a decrease in late spring and early summer,

an increase in midsummer which, in the present instance was even greater than that in winter and a marked decrease in the autumn. The curves for the parathyroid, pituitary and pineal glands are of a simple diphasic type with maximum values in midsummer and minimum values in the winter. While I am not now concerned with interrelations, I may

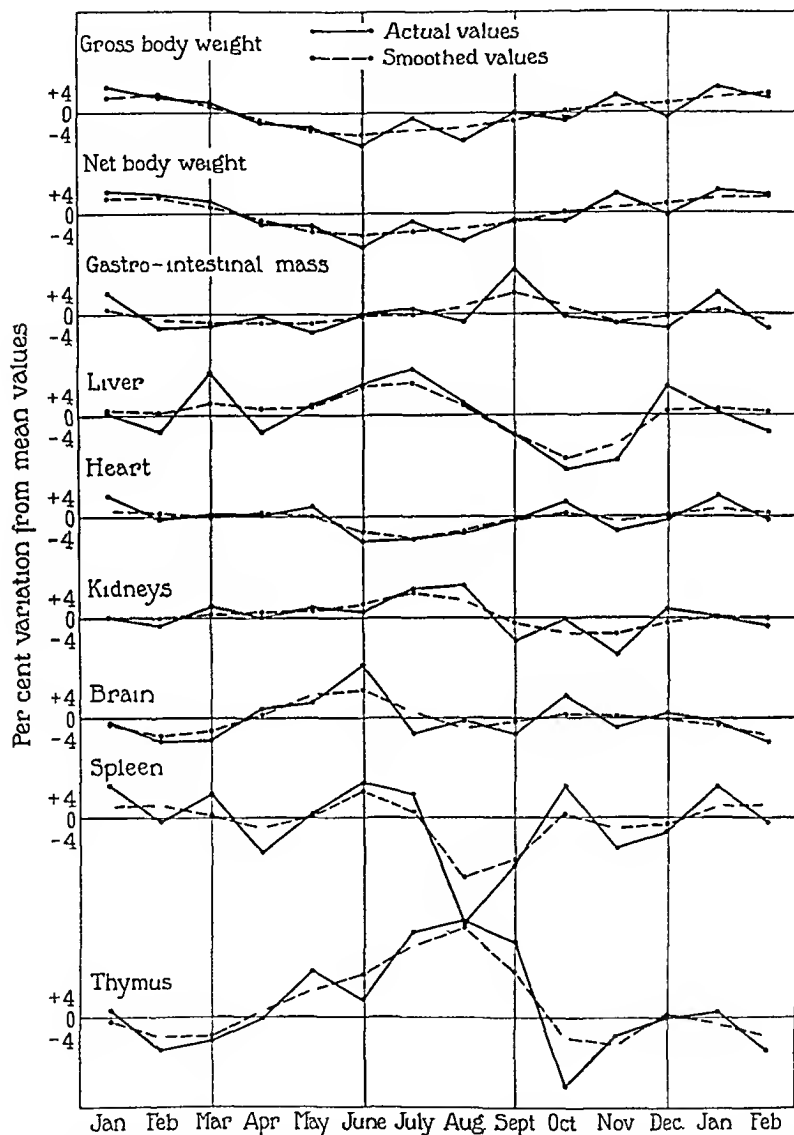


Chart 3—Variations of body and of organ weights per unit of body weight

call attention to the fact that in some instances the relation between organs is direct and in others inverse, or that for one period of the year the relation may be direct while for another it is inverse.

The variations shown may appear to be too complicated to permit of interpretation, but certain features of their meaning can be made clear by the use of a simple system of grouping and combination of

results For this purpose, the organs may be divided into three groups the first group including the heart, liver, kidneys and brain, the second, the endocrine glands and the third, the lymphoid organs<sup>2</sup> I shall assume that the organs of the body are provided in such numbers and

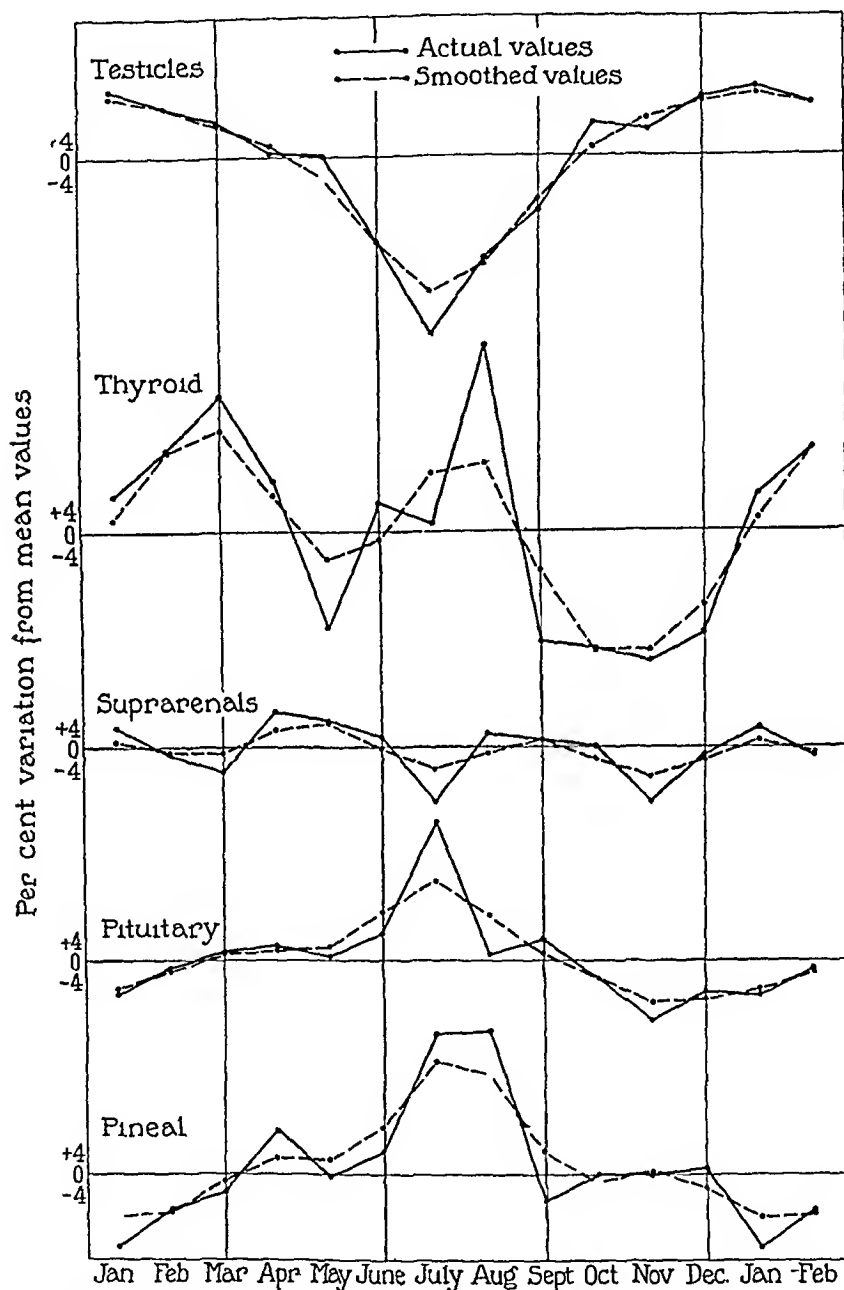


Chart 4—Variations of organ weights per unit of body weight

sizes as are necessary for the performance of their functions. If this is true, the organs should be dealt with so as to be given an equal value

2 The thymus is grouped with the lymphoid organs on account of its relation to the spleen, but without prejudice as to its relation to other organs. The gastrointestinal tract and testes are omitted, but their inclusion would not alter the results as given.

irrespective of size. In the present instance this can be done by combining the results for the organs of each group on the basis of the algebraic sum of the percentage deviations from mean normal values (chart 6). In this way, a single curve is obtained for each group of organs, but in these curves each organ has the same value, just as one assumes that it has in the body.

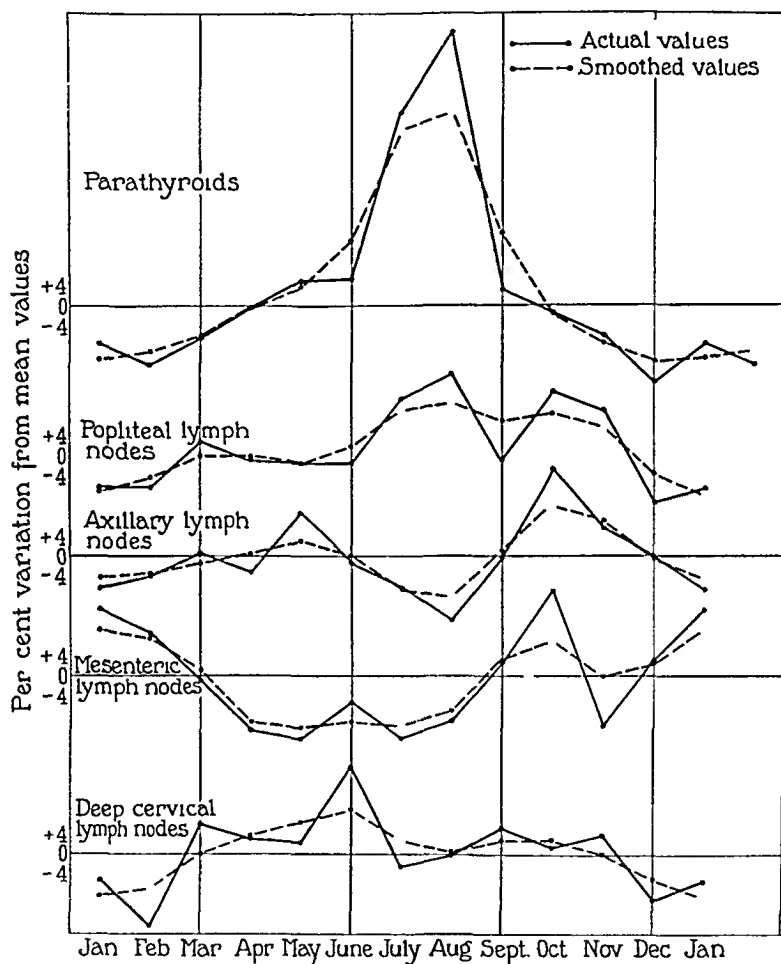


Chart 5—Variations of organ weights per unit of body weight

These curves enable one to visualize variations in terms of systems which differ somewhat in the character of their functional activities. Carrying this idea a step further, the three system curves may be combined, and thus a single expression is obtained of the relation that exists from month to month between the body as a whole and the total mass of organ tissue on which it depends for the maintenance of its various activities. This relation may be spoken of as the organ balance, and is expressed as a positive or a negative percentage deviation from a standard or a mean normal value. It is represented here as an

aggregate value, but in other places, it has been found more convenient to deal with it as a mean which, of course, does not alter the relation as here presented

The reduction of the organ-body weight relation to a simple expression of a positive or a negative balance places this feature of the seasonal variation in constitution on a basis that is easy to comprehend.

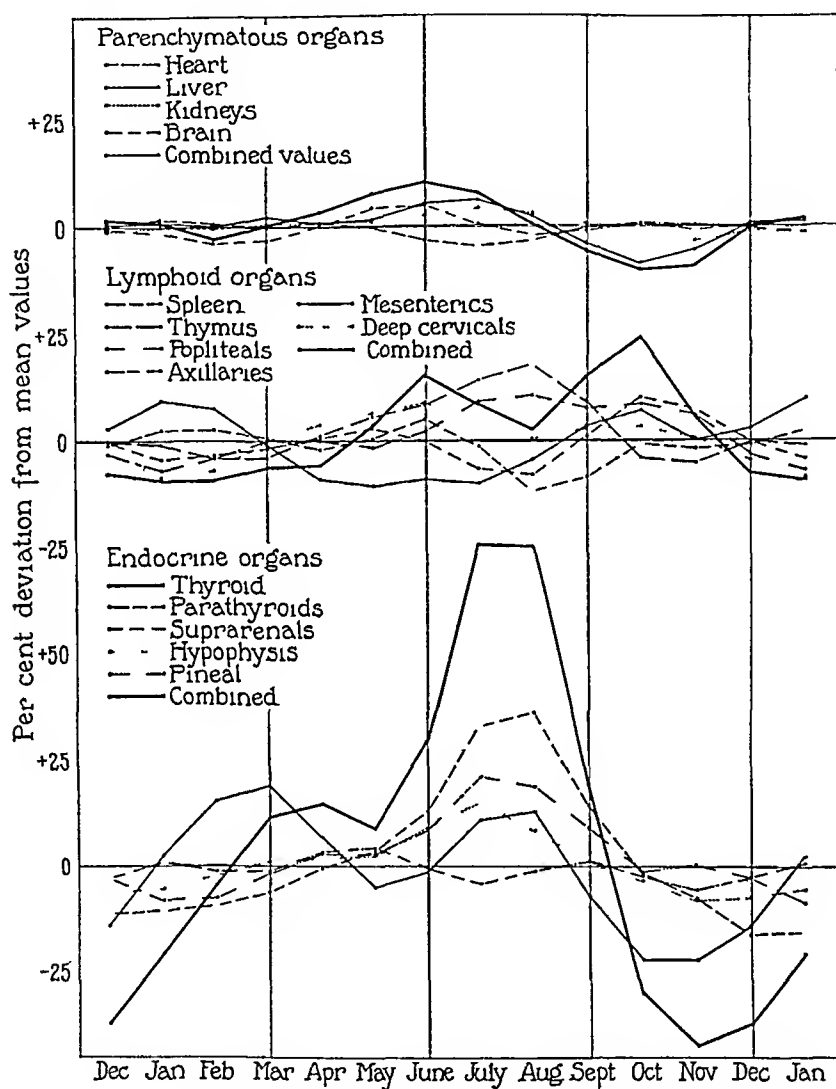


Chart 6—Integration of organ systems

If organic constitution has any functional significance, it is not difficult to imagine that with the changes in organ balance which occur from month to month there must be some changes in functional potentialities and that such changes might well include variations in susceptibility to disease

The increasing balance during the first half of the year, with an interruption of the progressive movement in the spring, and the decreasing balance during the second half of the year, with high values in

summer and low values in fall, are significant features of the seasonal variation. It will be noted that the changes in organ balance virtually parallel the curves for sunshine, or solar radiation, temperature, absolute humidity and other meteorological conditions (chart 8). However, while some organs tend to follow the direction of the seasonal trend, others show an interesting relation to the deviation of meteorological conditions from the normal (chart 9). In the present instance, the lymphoid system showed a direct relation with the deviations of the sunshine curve from September to March and an inverse relation from March to September.

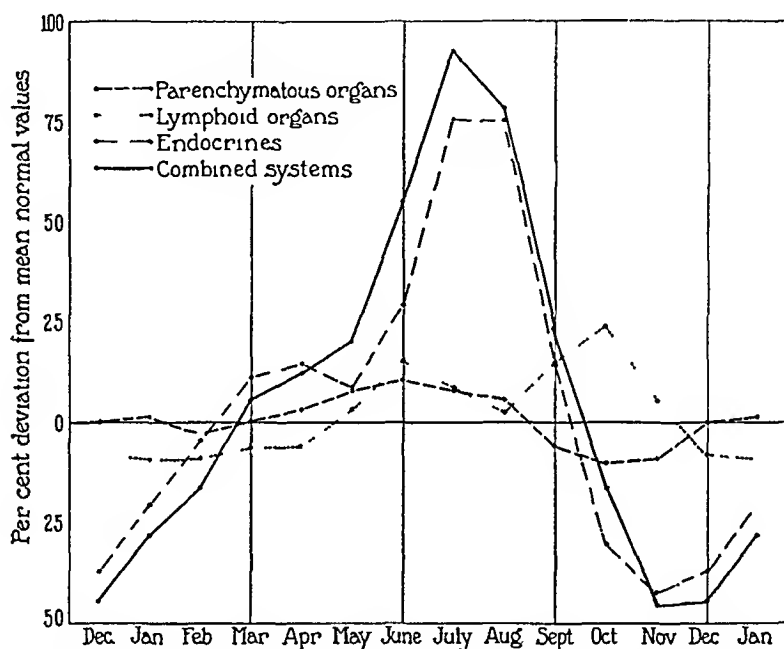


Chart 7—Combined system values—aggregate organ balance

It is thus evident that the relation between seasonal conditions and organ balance is not simple and quantitative. Moreover, the occurrence of variations in the weights of organs affects not only the organ-body weight relation, but the relation of one organ to another, or of one system of organs to another, so that the composition of the organ balance varies qualitatively as well as quantitatively.<sup>3</sup> For present purposes, this phase of constitutional variation may be illustrated by the relation between the endocrine and lymphoid systems expressed as a ratio. It is found that this relation varies in much the same way as the total organ balance, owing to the fact that the endocrine organs usually dominate the situation, but the variations in the lymphoid

3 Among the interrelations investigated by us, the only constant relation found is that between the pituitary and suprarenal glands

system are sufficient to produce an appreciable effect on ratio values, especially during the critical periods of spring and fall.

It must not be assumed, however, that the variations in organ balance repeat themselves in a perfectly methodical manner year after year. This is not the case. The time of occurrence of seasonal

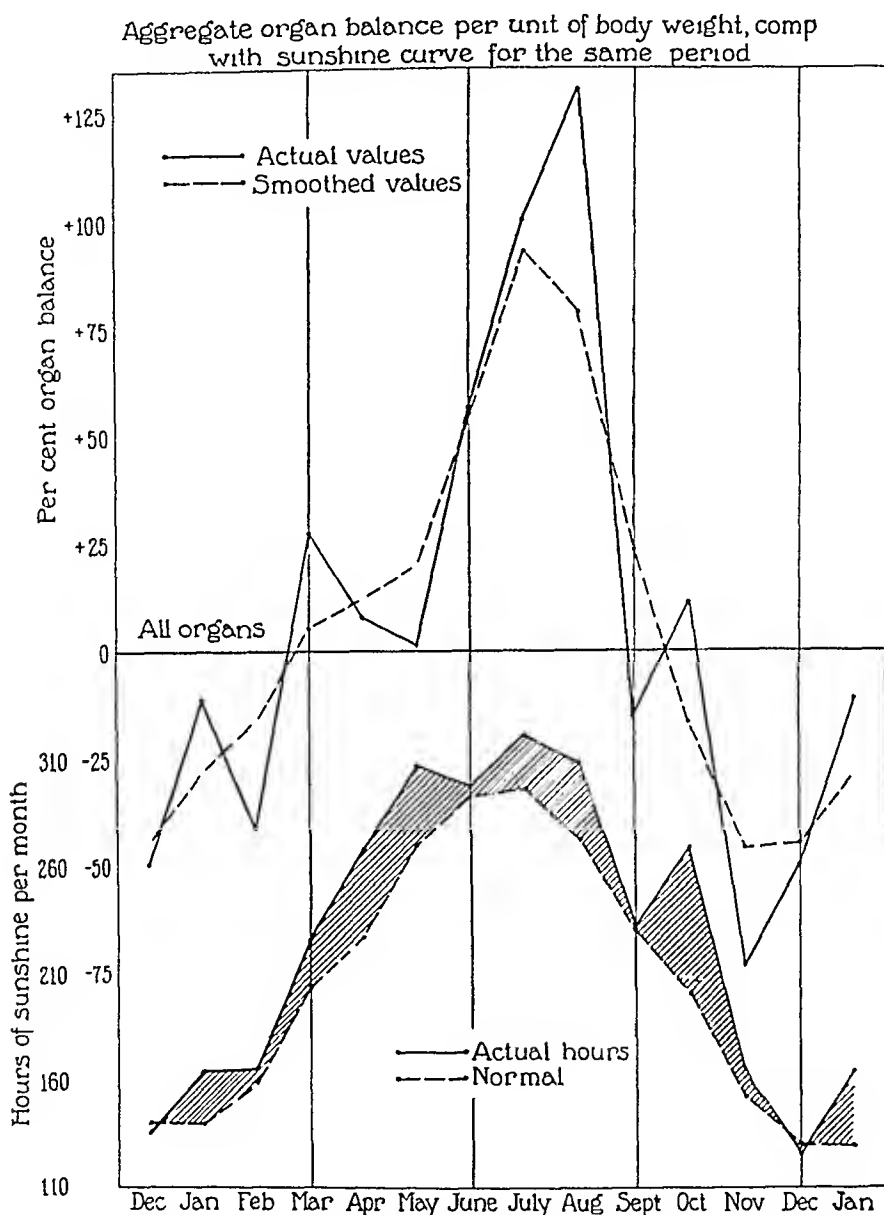


Chart 8—Aggregate organ balance per unit of body weight, compared with sunshine curve for the same period

variations and the magnitude of the values attained differ greatly, and the difference between years is just as important as the seasonal changes.

Constitutional differences are not confined to physical factors. There are also chemical differences, as shown by a study of the blood, and while it has not been possible to investigate this phase of the subject as in the case of physical constitution, the results are suggestive



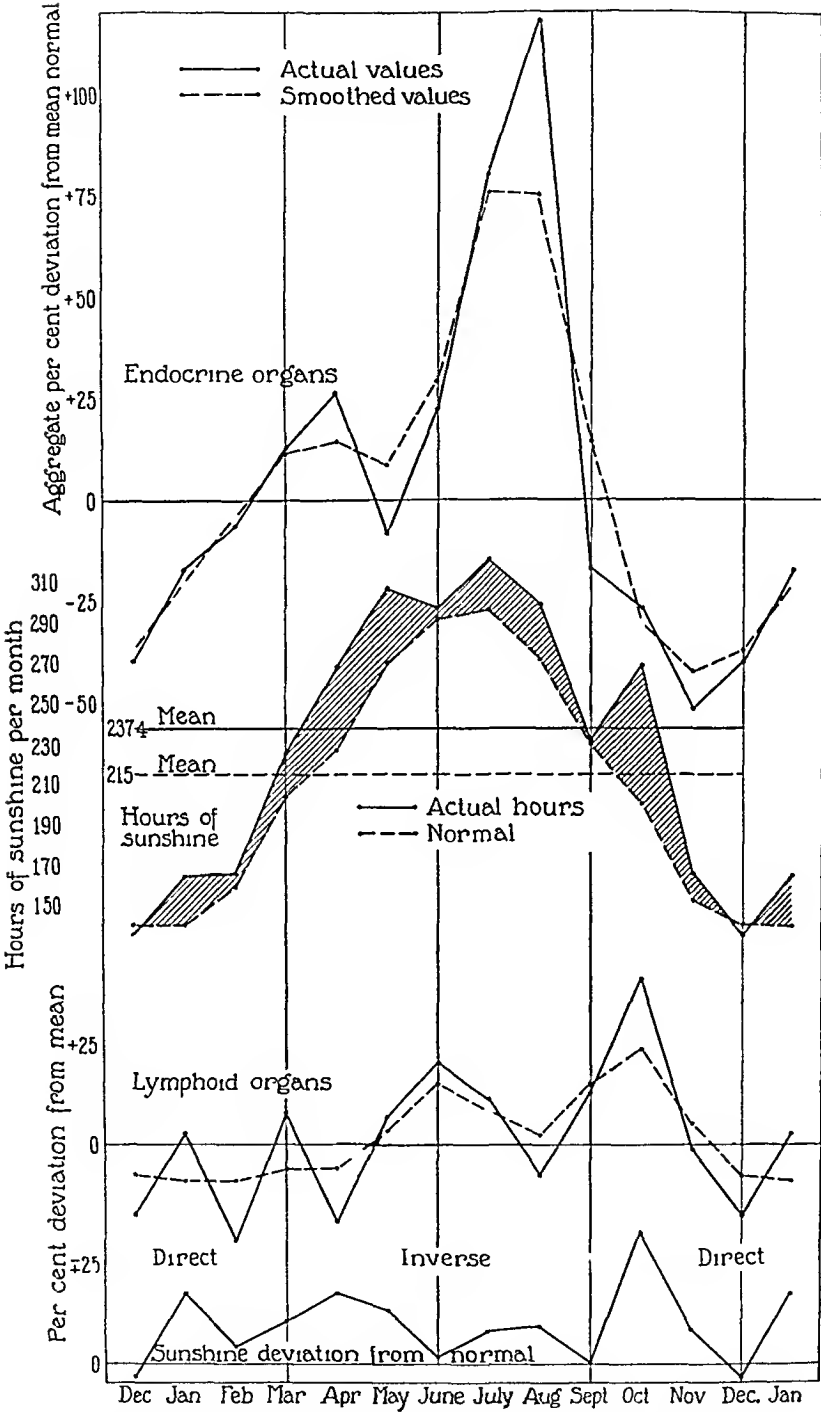


Chart 9—Variations of organ balance in relation to sunshine

These studies have been limited to four substances, serum calcium, inorganic phosphorus and the lipid phosphorus and cholesterol of whole blood. For convenience in this discussion, lipid phosphorus is estimated and spoken of as lecithin. The four substances mentioned form two couplets, the one organic and the other inorganic, taken

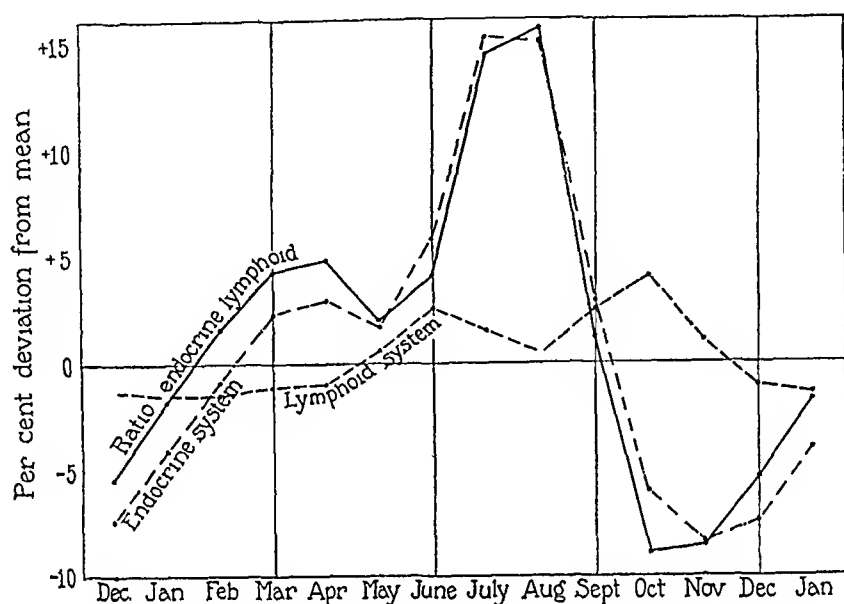


Chart 10—Relation of endocrine to lymphoid system

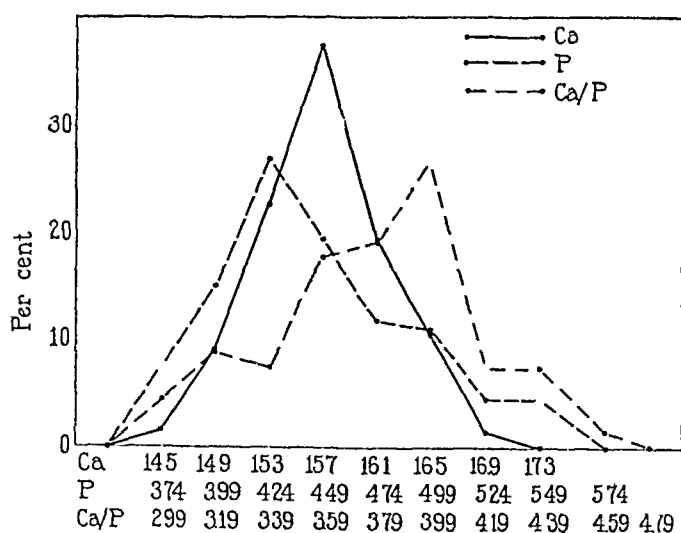


Chart 11—Distribution of animals according to the mean levels of calcium, phosphorus and the calcium phosphorus ratio

together, they present an interesting series of variations under normal and pathologic conditions which appear to be related to physical constitution on the one hand and to environmental factors on the other.

While the methods available for the determination of these substances in large series of animals are not sufficiently accurate to enable

one to draw conclusions from a comparison of single values (unless the differences are large), the results of repeated determinations, or of group determinations, may be used as unit values

To begin with, individual animals differ with respect to the mean levels of calcium, inorganic phosphorus, lecithin and cholesterol which they maintain in the blood just as they do with respect to the weights of organs or of any physical character. A classification of animals on this basis gives results which conform to the rule of thumb ratio of 1 3 1. This is shown by the distribution curves for sixty-eight animals based on the mean levels of calcium, inorganic phosphorus and the calcium-phosphorus ratio, as determined by systematic observations over a period of from four to eight months.

The concentration of these substances in the blood is also subject to frequent variation with a seasonal change of level. An example of the kind of conditions that may be expected is furnished by results obtained between October, 1927, and September, 1928 (charts 12 and 13). It cannot be assumed that these results represent the normal expectation, as conditions which prevailed during the period covered by these observations were distinctly abnormal (note sunshine curve). It appears, however, that the seasonal variation is more clearly defined among animals living outdoors than among those in the laboratory. In fact, the change from outdoor to indoor life may be sufficient in itself to induce alterations in the chemical composition of the blood which will completely obscure the seasonal variation.

The effect of these changes on the relation of one substance to another is of especial interest. For example, inorganic and lipid phosphorus. Between these two substances there is an almost perfect inverse relation, as a rule, when one increases, the other diminishes, while their sum tends to remain constant. In summer, it is the inorganic component that is high, while in winter the lipid fraction is high and the inorganic low. These relations hold not only for seasonal variations, but under a variety of conditions, and probably play an important rôle in such diseases as rickets.

Cholesterol and calcium also show a high correlation of the inverse order. Going still further, one finds that the ratio between cholesterol and calcium varies inversely with the ratio between lecithin and inorganic phosphorus, so that even small variations in the absolute amounts of these four substances are sufficient to produce marked changes in equilibrium with characteristic seasonal differences. Thus, it appears that in winter the ratio of cholesterol to calcium is lower than the ratio of lecithin to inorganic phosphorus, while in summer this relation is reversed.

Other conditions could be cited but this is sufficient to show that there are variations in the chemical composition of the blood which are

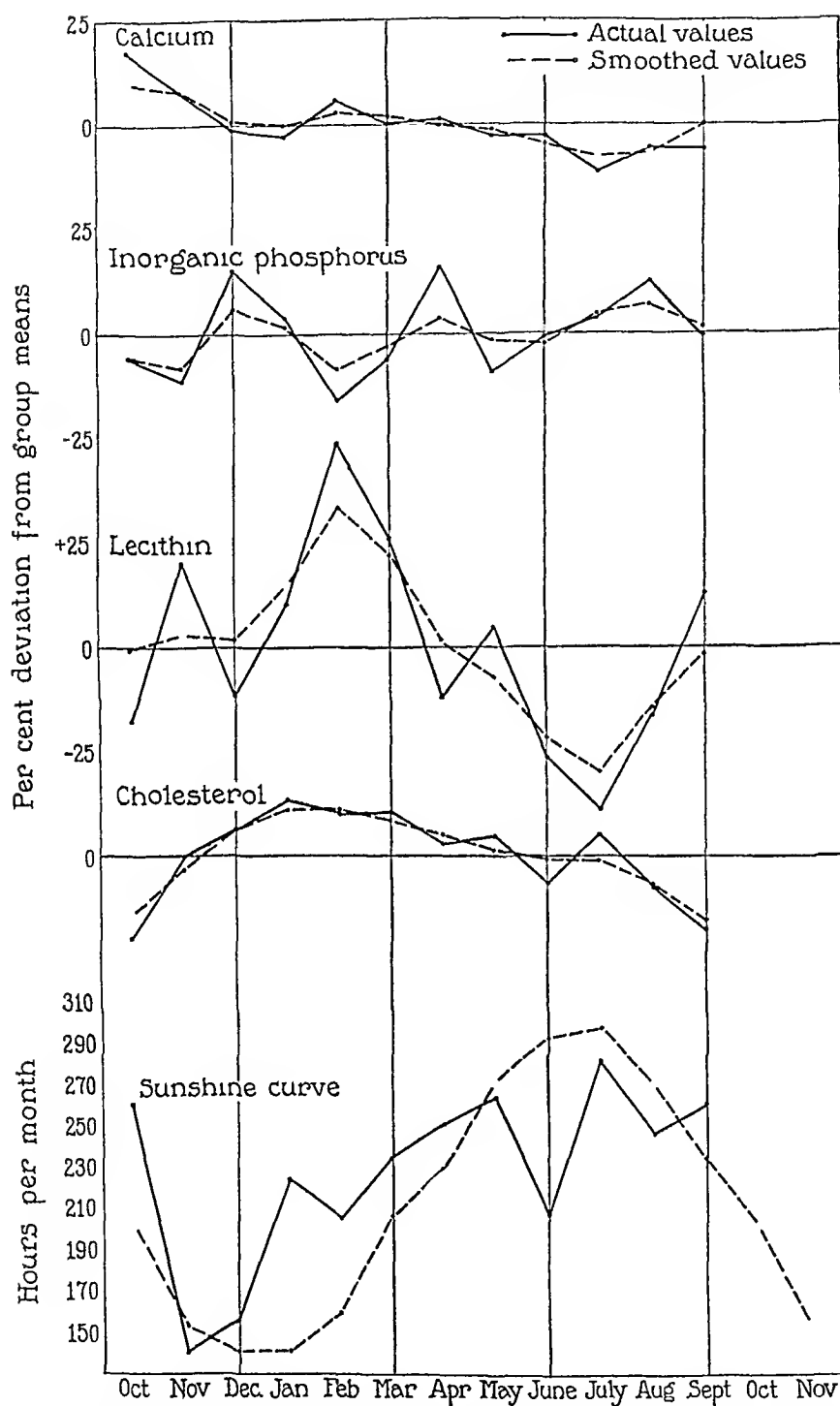


Chart 12—Variations in the chemical composition of the blood of animals when first brought into the laboratory

of the same general order as the variations in physical constitution. Similar studies have been made on the cellular elements of the blood, and while I am not prepared to discuss this phase of the subject at present, it seems that the results obtained will fit into the general scheme of behavior of other factors.

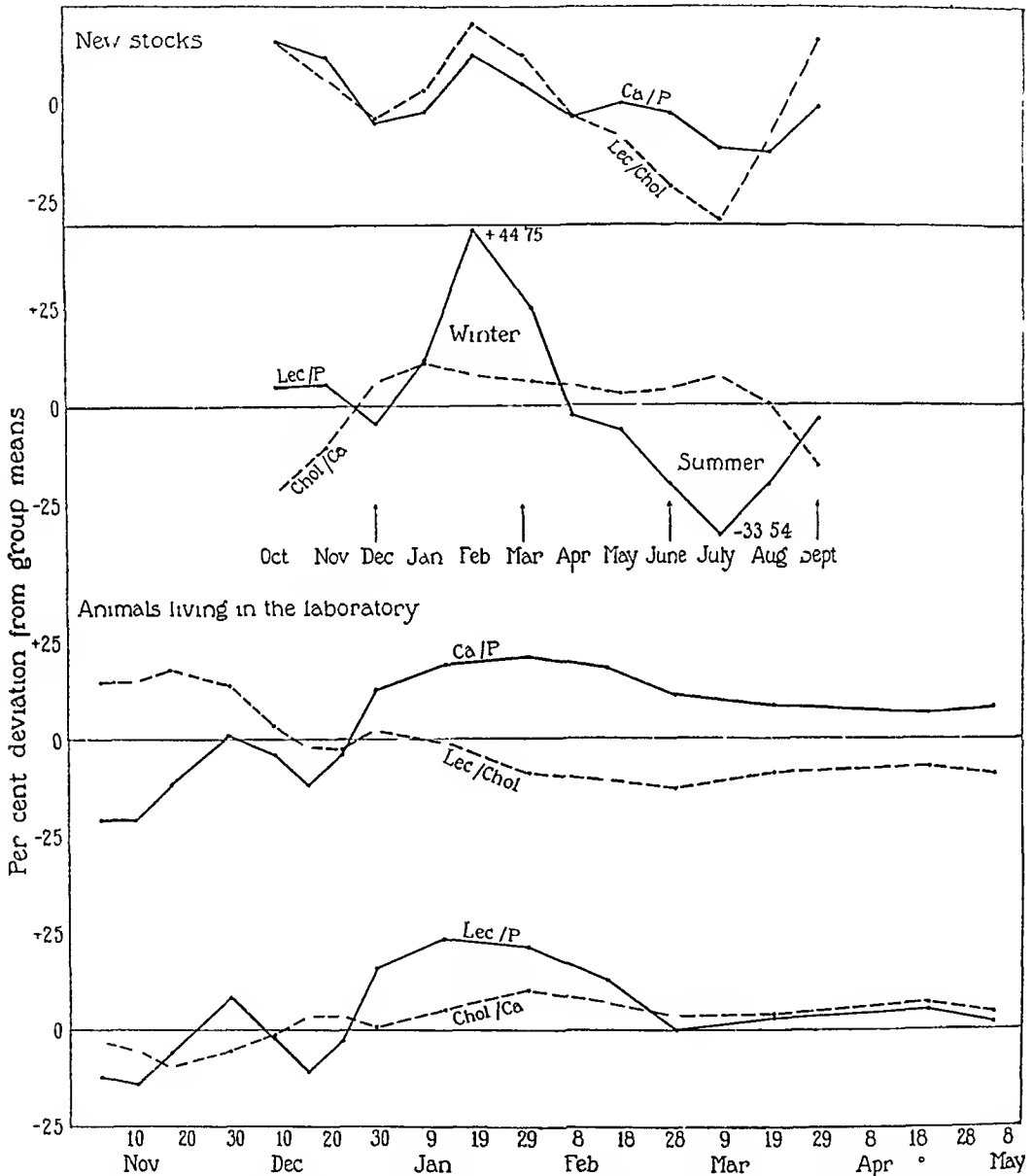


Chart 13—Variations in the relations of calcium, inorganic phosphorus, lecithin and cholesterol in the blood

At this point, attention may be called to the fact that in analyzing the results of a system of chemical variation as simple as that with which we have worked, there is abundant evidence to show that chemical constitution is a matter of total concentration and relation, just as in the case of organic constitution, and that, if sufficient data

were available, chemical constitution might be reduced to an expression comparable with that used for organic constitution. This is of especial interest in connection with variations in susceptibility to disease and in the reaction to disease. An excellent example of this condition is furnished by ticks.

So far, I have dealt with organic and chemical variations that are presented by animals as they are brought to the laboratory (chemical)

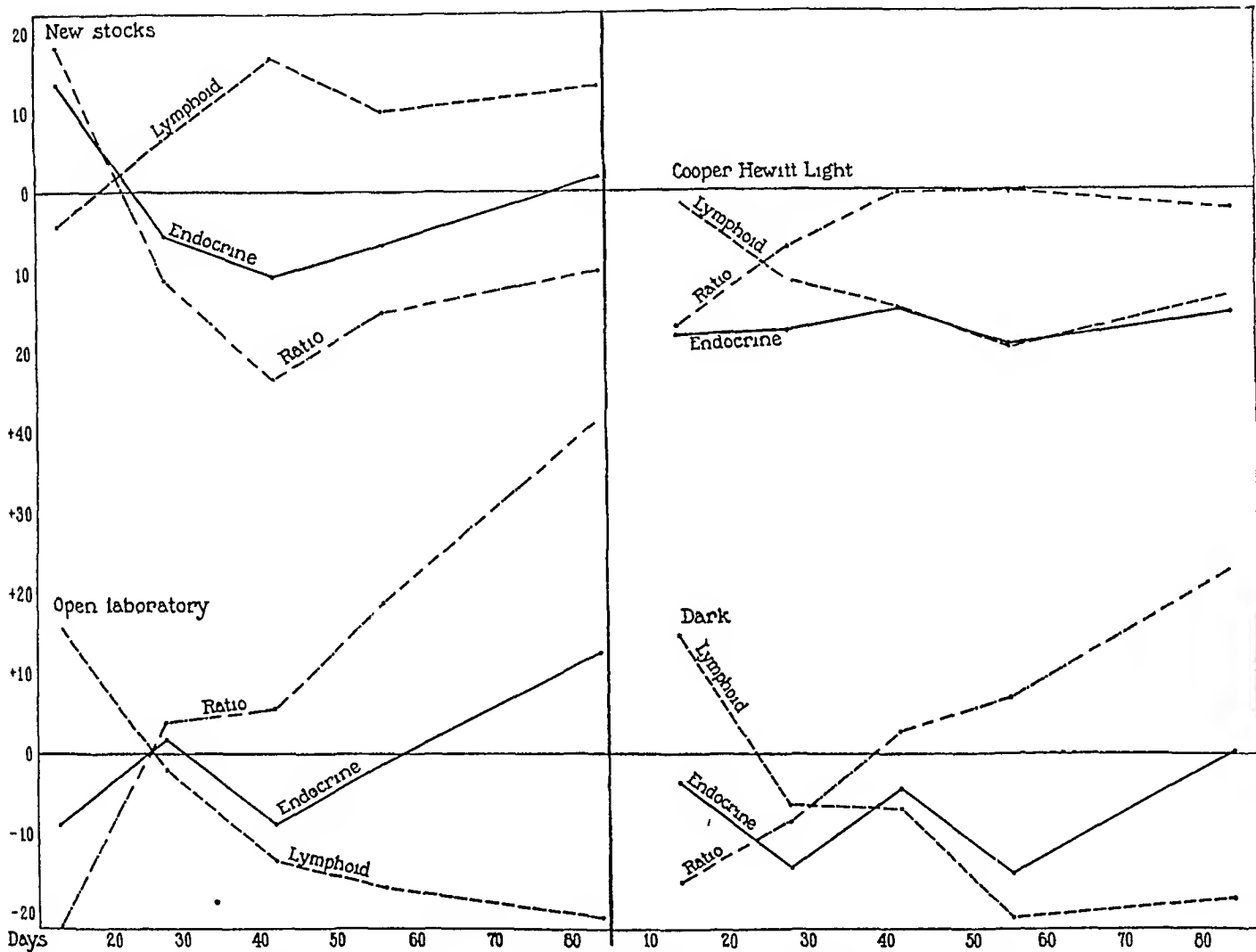


Chart 14—Influence of light environment on equilibrium of endocrine and lymphoid systems

or within a short time thereafter (organic constitution). It has been pointed out, however, that in addition to certain inherent differences in the constitution of animals, variations occur which suggest a relation to environmental factors such as sunlight. This, of course, does not imply that the relation to other factors is not equally close, but merely that there is a suggestion of a light relation. The influence of light on organic phosphorus is familiar to all, but less is known concerning

the effect of light on other constituents of the blood and very little as to its effect on physical constitution apart from phenomena of nutrition and growth, but it can be shown that light environment is capable of producing definite effects on both the physical and the chemical constitution

The effect on organic constitution may be illustrated by a comparison of concurrent results obtained for several groups of animals living under different environmental conditions. These results may be compared on the basis of the values obtained for organ systems rather than those for given organs, and with especial reference to the ratio of endocrine to lymphoid tissues. There are four conditions to be considered: (1) exposure to winter sunlight (outdoors), (2) exposure to filtered sunlight of the laboratory, (3) constant exposure to light from Cooper Hewitt lamps (low pressure mercury arcs in crown glass), and (4) exclusion of all light. Two of the conditions are subject to irregular variation, the others are fixed so far as the light is concerned. From time to time animals from each of these groups were killed and the organs weighed.

The weights of endocrine and lymphoid organs of animals exposed to unfiltered sunlight varied in such a way as to cause first a marked reduction and then a slight increase of ratio values, but the ratio remained subnormal. The changes that occurred among animals in the open laboratory and among those in the dark, however, were in the opposite direction and the ratio was increased to a point well above the mean normal level (standard value). The change under open laboratory conditions was greater than that in the dark. The outstanding feature of the effect produced by the Cooper Hewitt light was the establishment of an essentially normal equilibrium which was maintained for a considerable time despite the occurrence of variations in both systems of organs.

This effect of light environment on organic equilibrium is of especial interest because chemical equilibria are affected in a similar manner. This is clearly shown by the influence of light on blood calcium and inorganic phosphorus (chart 19). Among animals exposed to sunlight, calcium and inorganic phosphorus vary so that, other conditions being equal, the ratio of calcium to phosphorus is inversely proportional to the amount of light received. Of course, ultraviolet light is the prime but not the sole factor in determining these changes. When animals are brought into the laboratory and are thus deprived of ultraviolet radiations, two things happen. In the first place, the change in the mode of living produces a disturbance of equilibrium. When the effects of this influence have subsided, however, inorganic phosphorus tends to decrease, while calcium usually increases, so that

the ratio of calcium to phosphorus increases just as the ratio of endocrine to lymphoid tissues increases under similar circumstances

If animals are exposed to Cooper Hewitt light or to the long wave length radiations of neon light, the increase in the ratio of calcium to phosphorus may be appreciably diminished, and there is a tendency to

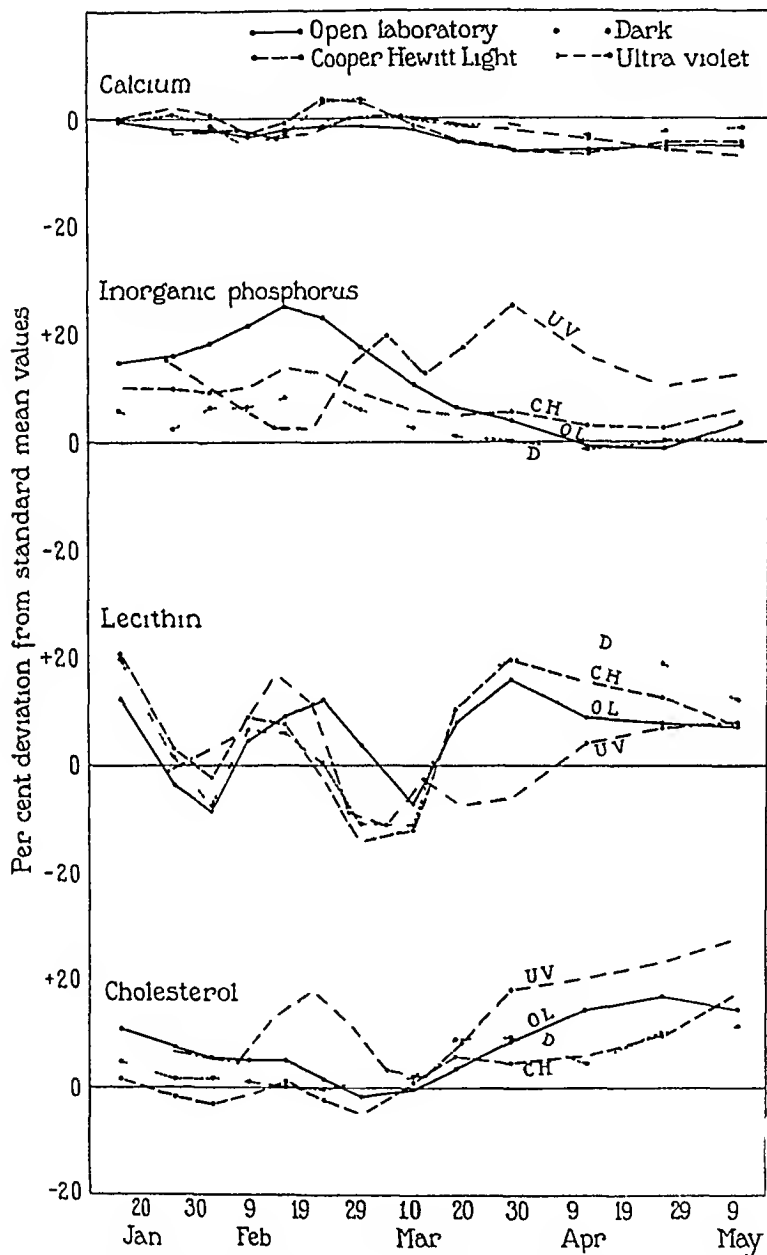


Chart 15—Influence of light on chemical composition of the blood

preserve a more uniform level. Animals in the dark, on the other hand, show an accentuation of the decrease in inorganic phosphorus and an increase in calcium with a higher ratio between the two substances. These effects are comparable with those on organic constitution and they are also comparable with differences found in animals of different ages.



The influence of light on the lecithin and cholesterol content of the blood and on the ratios of these substances to inorganic phosphorus and calcium is even greater (chart 15). For example, it was found that animals irradiated with the quartz mercury arc, at considerable distances (45 meters) and without removal of hair, showed an increase of inorganic phosphorus, a decrease of lipid phosphorus, an increase

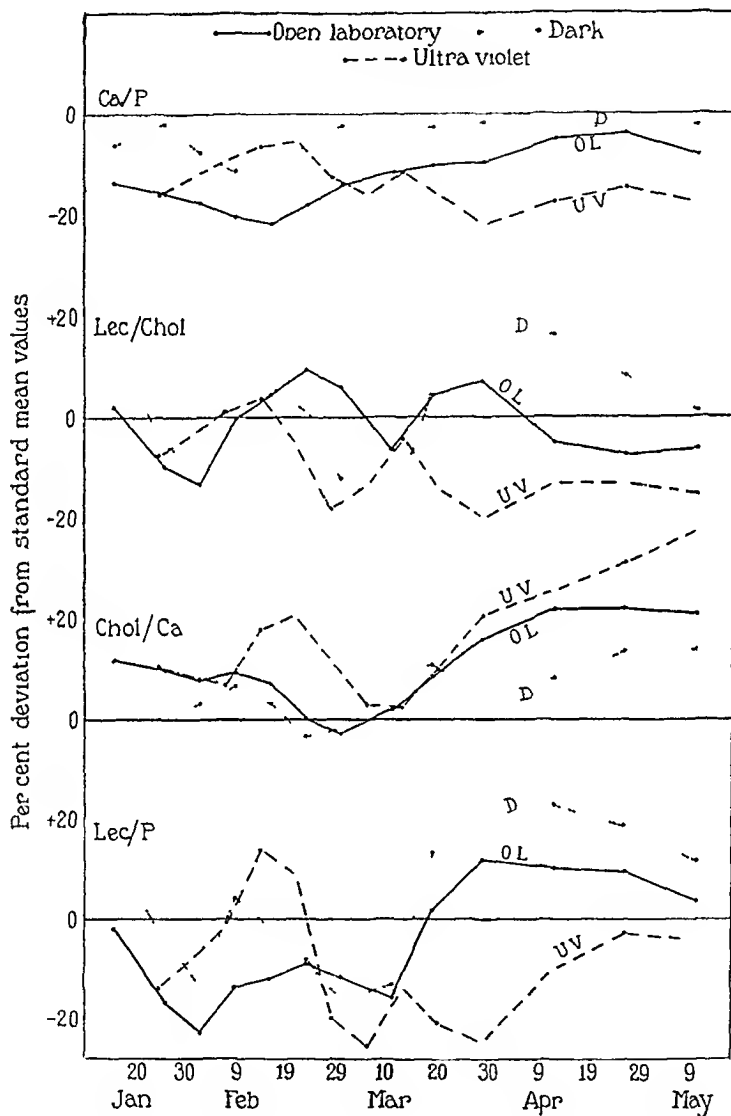


Chart 16—Influence of light on chemical equilibria in the blood

of cholesterol and a decrease in calcium. Complete exclusion of light had an opposite effect, while exposure to diffuse filtered sunlight or to Cooper Hewitt light produced intermediate results.

Similar conditions obtained with respect to ratio values (chart 16). In all cases, opposite effects were produced by ultraviolet irradiation and darkness. Thus, under the influence of ultraviolet light, the ratio between lecithin and inorganic phosphorus decreased while the ratio of

cholesterol to calcium increased, simulating conditions which prevail in summer, while exclusion of light produced an opposite effect with the development of conditions more analogous to those of winter

It is extremely difficult to establish a mathematical correlation between the effects produced by environmental influences on physical and on chemical constitution owing to the limitations of methods now available. There is definite evidence of the existence of such a relation, but for the present it seems best to let the matter rest on the basis of analogy

#### EFFECT OF PHYSICAL AND CHEMICAL CONDITIONS ON SUSCEPTIBILITY TO DISEASE

I come now to the question as to whether such physical and chemical conditions as those described have any bearing on susceptibility to disease. In the study of this problem, two chronic diseases have been used, syphilis and neoplasia. These diseases offer some advantages over the more acute infections. In the first place, they present every gradation in the severity of disease from an extremely mild to a uniformly fatal condition, and the clinical course of disease can be followed with reasonable accuracy from the time of inoculation to its conclusion. An opportunity is thus afforded for a comparison of many phases of the reaction over a considerable period. Variations in the course of disease can be measured qualitatively and quantitatively, in terms of the rate of progress of the disease or of the frequency of occurrence of a given condition, or in terms of the number and distribution of lesions of a given type. Moreover, while the incubation period of primary lesions may be influenced by dosage or by the growth activity of the cells or organisms used for inoculation (which in reality is a matter of dosage), the subsequent course of events is not affected by slight differences in these conditions. It is thus possible to eliminate the troublesome factor of dosage and to reduce the problem to the basis of factors represented by the host, on the one hand, and the pathogenic properties of the causative agent on the other. It makes no difference whether one regards the results of the interaction between these two sets of factors as an expression of susceptibility, of resistance or of virulence, the term used does not affect the results, and one's interest, for the present, is in the results and the relation of these results to known constitutional conditions.

Bearing this in mind, I shall consider what happens when animals are inoculated with *Treponema pallidum*. To begin with, there is a variable period of incubation, then a lesion develops at the site of inoculation and for a time increases in size. The growth of these lesions then ceases, some show a sudden development of edema followed by retrogressive changes, constituting a critical reaction, while others remain stationary or undergo partial resolution without crises. At any rate,

there is a period of quiescence or inactivity, constituting a second incubation period, then generalized or secondary lesions appear in some animals but not in others. Finally, all lesions undergo resolution, the animal recovers and the infection becomes latent. There are, thus, two

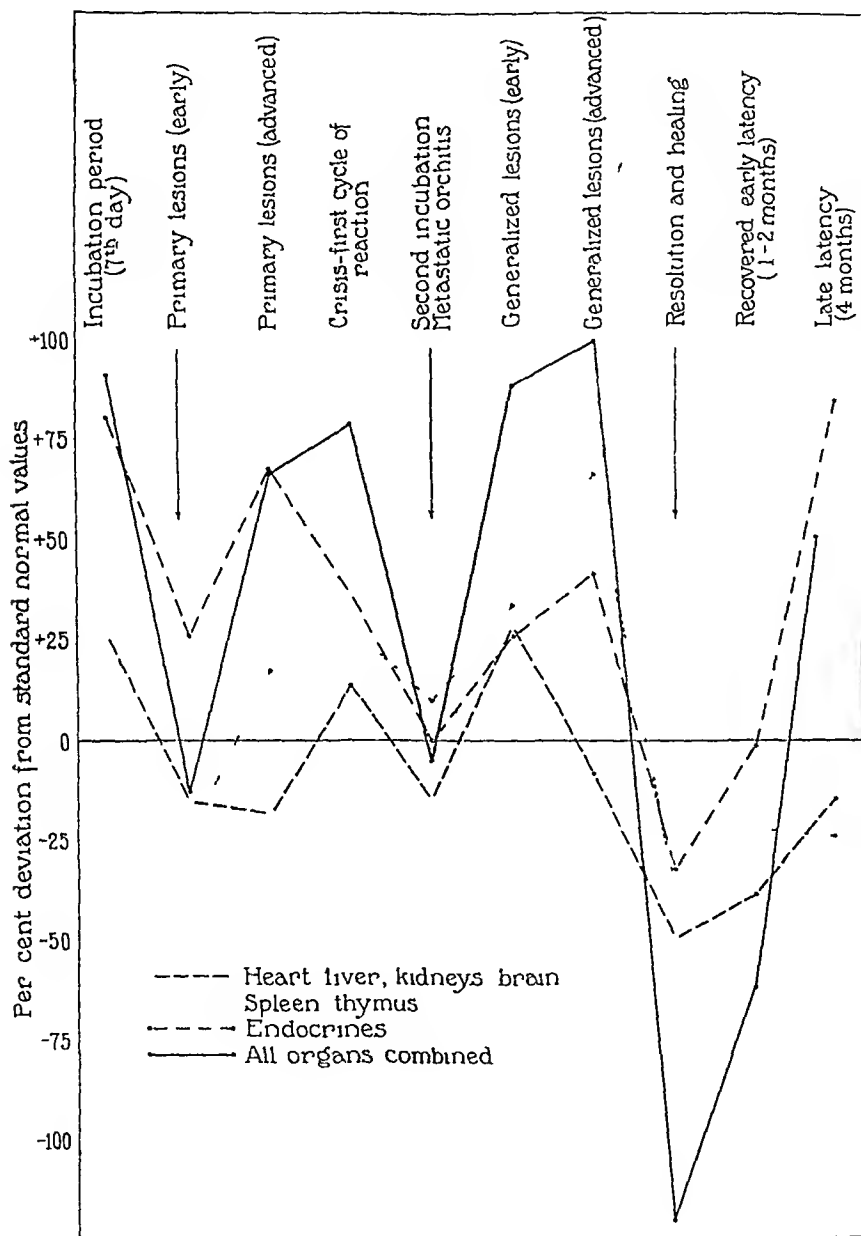


Chart 17—Organ balance in experimental syphilis of moderate severity—aggregate values

or more periods of development of the lesions, two or more periods of incubation or quiescence and two or more periods of resolution, marking the development of immunity and the termination of the active course of disease

This is the clinical course of events, but there are equally striking changes in physical constitution which affect the organ-body weight relation on the one hand, and the relations between organs on the other, (charts 17 and 18) The changes in physical constitution parallel the clinical course of disease throughout, with periods of increasing and decreasing organ balance corresponding with the periods of activity and quiescence of lesions, and terminate with the development of a state of organic equilibrium in the immune animal which differs from that

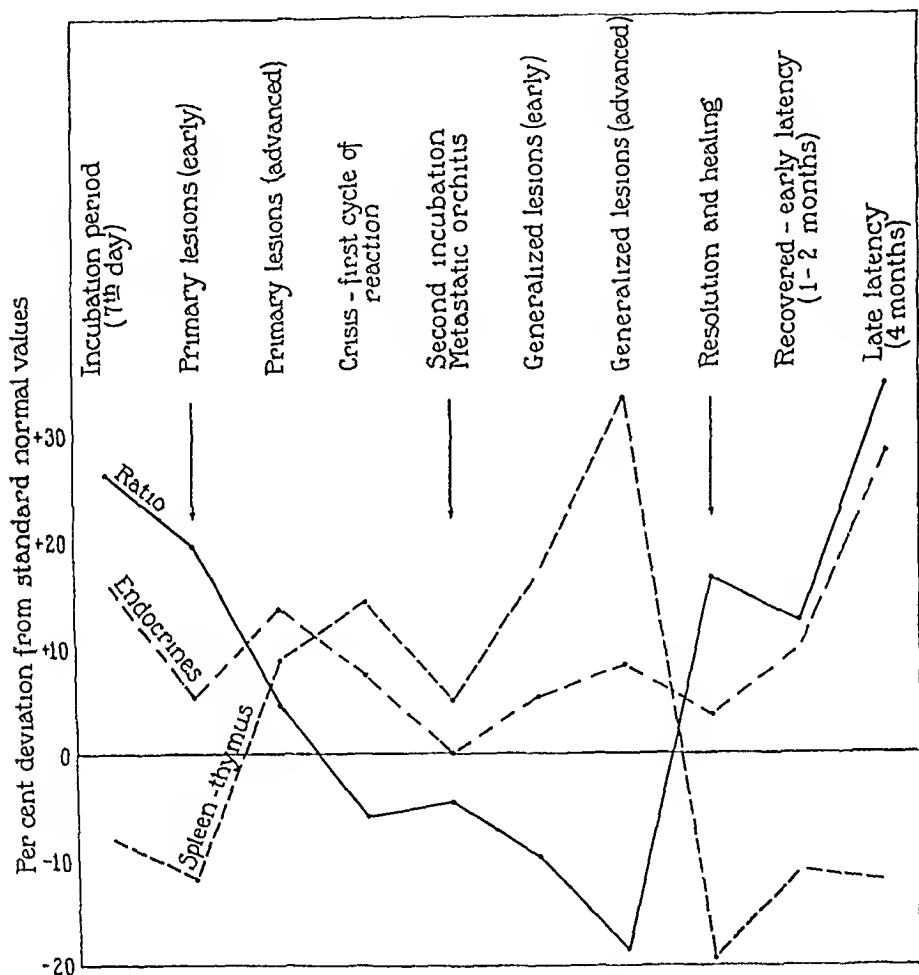


Chart 18—Endocrine-lymphoid equilibrium in the reaction to syphilitic infection

of the normal animal. The exact nature and extent of the change that occurs vary with the severity of the disease. Since visceral lesions do not occur in rabbits, these changes must be regarded as systemic reactions to infection.

In the case of the tumor, inoculations are made with a homogeneous cell emulsion, but the results are extremely variable. Some animals are completely refractory, others develop a benign tumor, while still others develop tumors which metastasize to all parts of the body and kill within from three to four weeks from the time of inoculation.

Animals with tumors show a series of changes in organic constitution analogous to those seen in syphilis. Thus, in the case of animals with benign tumors and of animals that recover, there is a tendency to develop a strongly positive organ balance, while in animals with malignant tumors, the balance becomes negative.

In this connection, it is of interest to note that animals which are immune to one of these diseases show an increased resistance to the other and, conversely, animals which are highly susceptible to one disease are highly susceptible to the other, that is, a classification of animals on the basis of susceptibility to one disease holds also for the other.

A similar situation obtains with respect to changes in the chemical composition of the blood. In this instance, I wish to emphasize especially the importance of changes which lie entirely within the so-called limits of normal and are usually regarded as of no significance. An interesting example of this condition is furnished by the calcium-phosphorus equilibrium in the reaction to syphilitic infection (charts 19 and 20). The points to which I wish to direct attention are (1) the relation between the development of lesions as manifestations of the state or progress of the reaction to infection and the occurrence of changes in the chemical composition of the blood at corresponding times especially at the time when new lesions cease to appear, (2) the difference between the calcium-phosphorus equilibrium of animals that have suppressed their infection and normal animals living under the same conditions.

As I have already pointed out, one cannot grasp the full significance of such changes as those seen in these experiments without considering both concentration and relation. It may be seen, however, that the trends of the curves for inorganic phosphorus and for the calcium-phosphorus ratio in particular show a definite relation to the course of disease. It is also of interest to note that the precise nature of the change differs somewhat with conditions that exist at the time of inoculation, with the severity of the disease and with the conditions under which the animals are living. The changes that occur during the early stages of the infection are variable, but as the progress of the disease is arrested, there is usually an increase in the calcium-phosphorus ratio which may be caused by either an increase in calcium or a decrease in inorganic phosphorus. This is followed almost immediately by a reversal of the direction of these curves: inorganic phosphorus increases and the calcium-phosphorus ratio decreases so that in the immune animal not only are the values obtained for calcium and phosphorus nearer the mean normal levels than those for normal animals living under the same conditions, but they show less fluctuation.

The results as here presented are for groups of ten animals each. The relation between the course of disease and the chemical composition of the blood is brought out much more clearly by comparing the results for individual animals, but it is not obscured by grouping the results despite the fact that the course of disease in different animals is variable and the changes in the blood of one not infrequently counterbalance those of another.

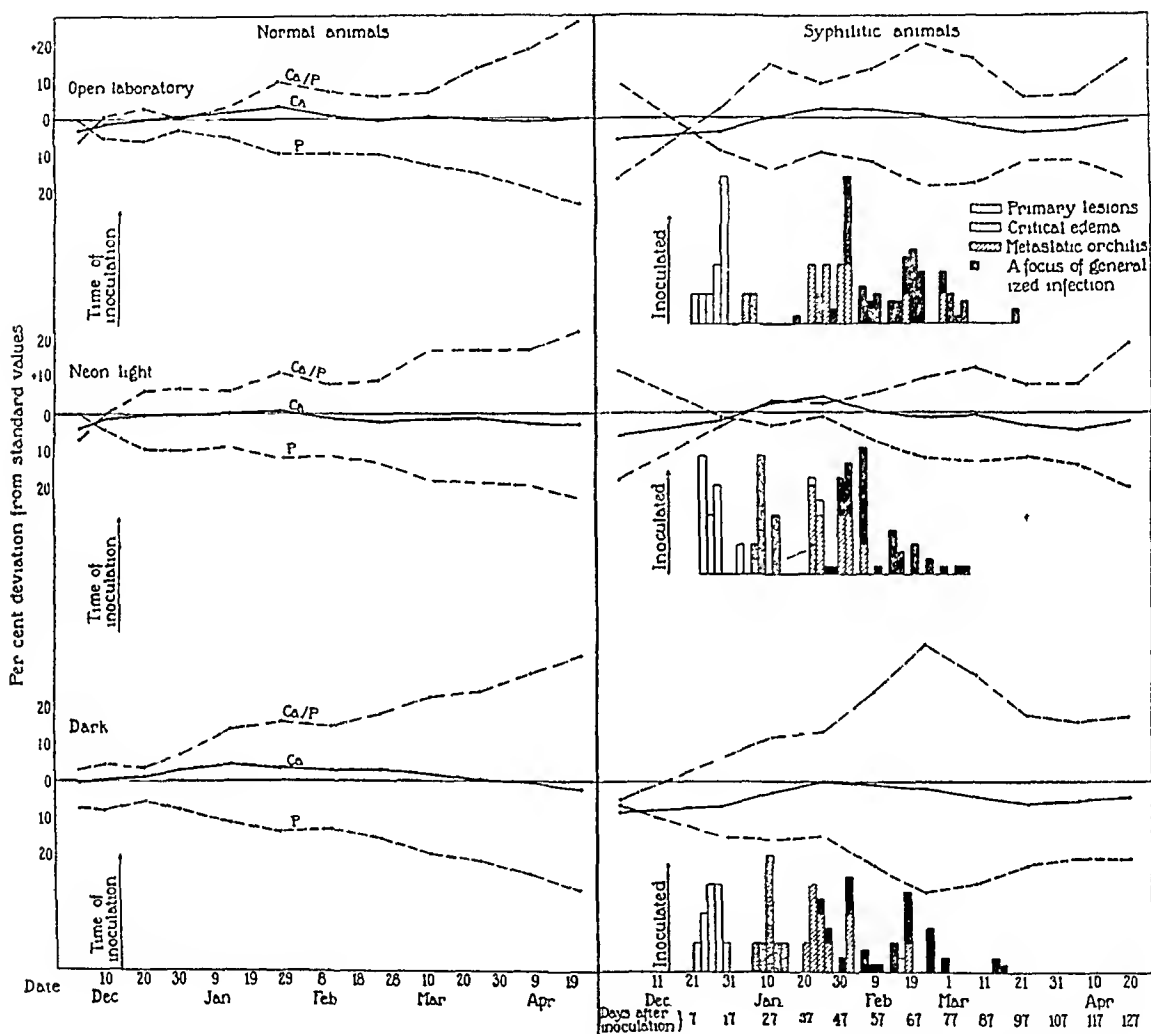


Chart 19—Relation between the course of syphilitic infection and the phosphorus equilibrium in the blood under different environmental conditions

It is not certain whether the changes in the calcium-phosphorus equilibrium are to be regarded as direct results of the reaction to infection or are referable to changes in other substances, such as lecithin and cholesterol which show an even greater response.

In animals with tumors, it is more difficult to establish a definite relation between chemical variations and the reaction to disease. Marked alterations are obtained in the composition of the blood with clearly defined differences between animals that recover and those that die,

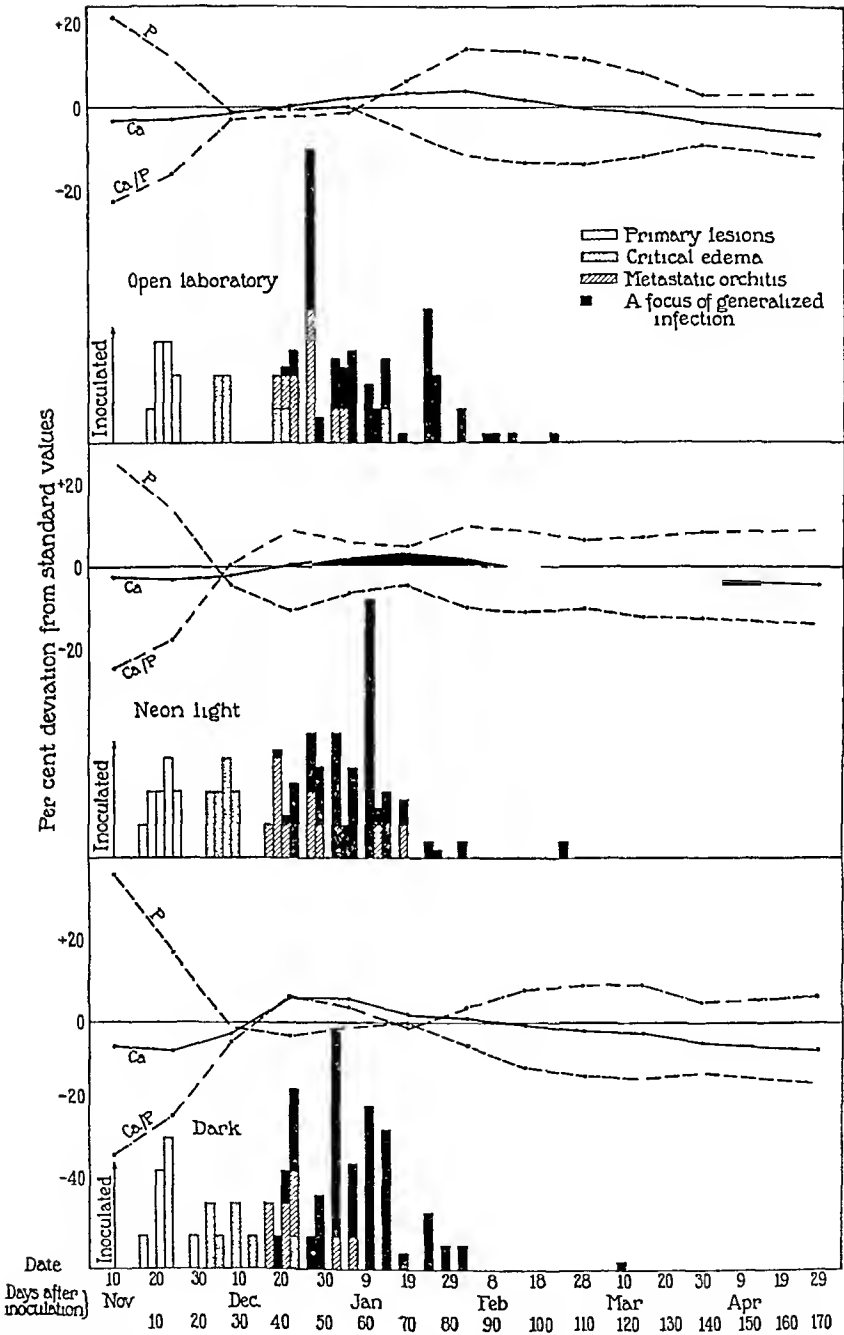


Chart 20—Relation between the course of syphilitic infection and the calcium-phosphorus equilibrium in the blood under different environmental conditions

but the interpretation of results is complicated by the localization of metastases in important organs. It can be said, however, that in the fatal cases there is a marked terminal increase in inorganic phosphorus and a decrease in calcium, with an increase in cholesterol and a decrease in lecithin, animals that recover show an opposite result.

The type of change that occurs in the blood of syphilitic animals and apparently also in animals with tumor, is of especial interest in that the reaction of recovery shows a tendency to revert to and to maintain a form of equilibrium which is usually associated with a particular type of organic equilibrium, on the one hand, and with certain environmental influences, on the other, both of which are characterized by seasonal prevalence and comparatively low susceptibility. It is surprising that, merely by the use of systematic observations, differences of the magnitude of those concerned in most of these reactions can be shown to bear such a close relation to a reaction to disease. After all, it is not the magnitude of a result that determines its significance but the relation which a result bears to something that is known to be significant.

Reversing the order of procedure, it has been found that the course of disease may be influenced in a definite direction by the use of measures which disturb organic equilibrium directly, as by the removal of a part or the whole of some organ, or by interference with the coordinating mechanism. Thus, removal of the thyroid greatly increases the malignancy of the tumor and the severity of syphilitic infections, but removal of only a part of the thyroid produces an opposite effect, while extirpation of ganglions or of parts of the nerves of the cervical sympathetics also affects the course of disease.

In like manner, the course of disease may be affected favorably or unfavorably by chemical agents which act not on the parasite but on the host, such as the iodides, or by the use of conditions which involve nothing more than a difference in light environment. As I have pointed out, light affects both physical and chemical constitution in a manner which, under certain circumstances, might be expected to increase the severity of disease and under other circumstances, to diminish it. As will be seen later, the results obtained agree with expectations based on the assumption of a constitutional effect of light.

#### ACTUAL RELATIONS BETWEEN CONSTITUTIONAL STATES AND SUSCEPTIBILITY TO DISEASE

So far, I have discussed variations in physical and chemical constitution of individual animals and of animal populations, the effects of disease on constitution and the effects of constitutional disturbances on disease. I come now to a consideration of the actual relations that obtain between given constitutional states, on the one hand, and



susceptibility to disease, on the other, as measured by the incidence and severity of reaction phenomena

I shall consider the distribution of various types of reaction among syphilitic animals, using the occurrence of generalized lesions as the basis of classification. In my experience, the incidence of generalized syphilis in rabbits varies from about 20 to 100 per cent, with a mean of approximately 60 per cent (unilateral testicular inoculation with the Nichols strain of *T pallidum*). The number of lesions or foci of infection is also variable, so that by actual count a numerical classification of animals can be made which corresponds with the extent of the lesions presented.

If the incidence of generalized syphilis is used as the basis of classification animals are divided into two groups. As approximately 40 per cent of all animals show no generalized lesions, the reaction displayed by these animals is not measurable on this basis, they are, so to speak, submerged. The remaining 60 per cent, however, give a distribution curve comparable to the diminishing segment of a normal bell-shaped curve which suggests that if the reaction of the submerged fraction could be classified accurately, the resulting distribution would be much the same as that for organ weights or for other physical or chemical characters (chart 21, *A*).

Since, at times, the incidence of generalized syphilis does reach 100 per cent, it is possible in such instances to classify the reaction of all animals, and when this is done one finds that the distribution curve is in reality a normal curve with a positive skew and is of the same order as the curves for constitutional distribution with the same 1 3 1 ratio (chart 21, *B*). By comparing the curve based on mean susceptibility with the curve for high susceptibility, one finds that the main difference is in their position on the susceptibility scale. Experience has shown that the distribution of persons about the mean or mode does not vary with the severity of the disease. During periods of transition the scatter is increased, but the group as a whole is moved up or down as the case may be.

This analysis brings out two important points: (1) that the factor of susceptibility is distributed in accordance with the same principles that govern the distribution of physical and chemical characters and (2) that the distribution curves for susceptibility and constitution are of the same type as the so-called epidemic curve.

An analysis of the variations of group reactions is also instructive. The significance of the occurrence of periodic increases and decreases in the severity of disease may be shown by a comparison of the results obtained for tumor malignancy and organ balance covering the same period. As a matter of fact, the animals used for the two sets of experiments were taken from the same stock—one lot was killed for a study of organ weights, the other was inoculated with the tumor.

Tumor malignancy may be reduced to the basis of a simple numerical expression by the use of two factors, namely, the incidence of metastases of malignant tumors among the animals of a group and the extent of the metastatic involvement. The latter condition is determined at autopsy by a systematic enumeration of the organs and parts of the body in which metastases occur.

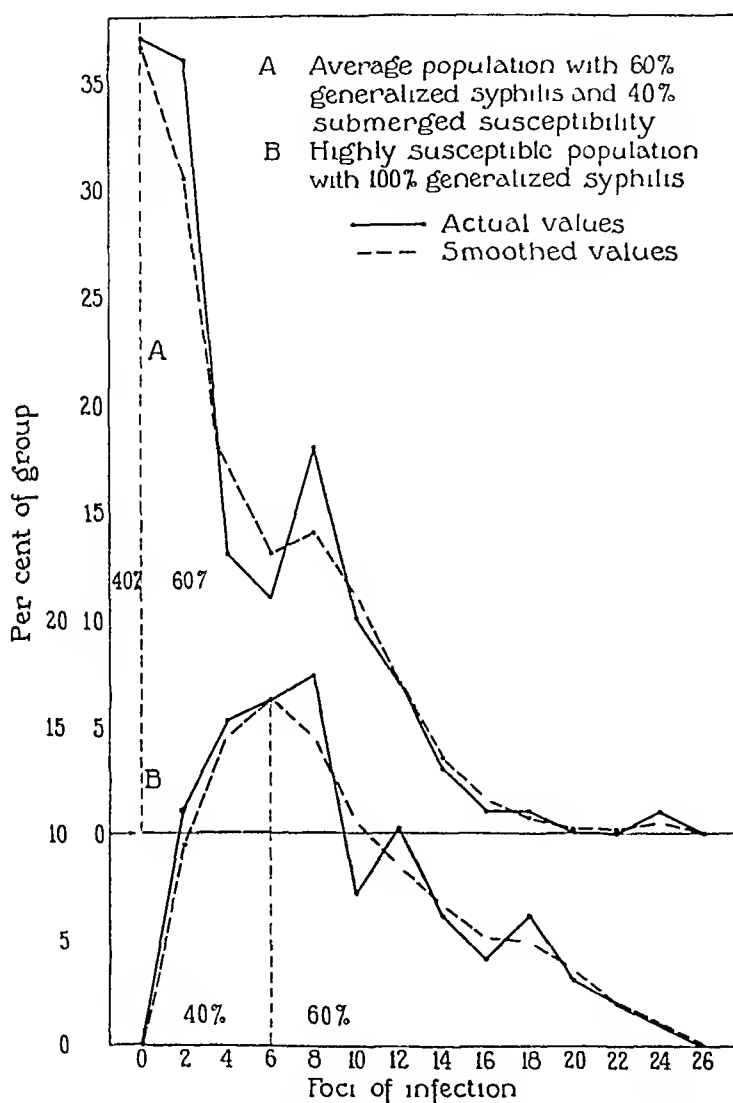


Chart 21—Distribution of individual susceptibility to syphilitic infection

If the results for the three years are reduced to the basis of a single year, as was done in the case of the weights of organs, it is found that both the incidence and the distribution rates show distinct seasonal variations with high points in the late winter, early spring and fall, the values for the summer months are much lower (chart 22). It will be noted, however, that the high and low points of the two curves do not coincide, but a change in one tends to precede a change in the other indicating that there is some difference between the factors of prevalence.

and severity True malignancy is expressed more accurately by a combination of the values for incidence and distribution

The curve obtained in this way does not differ greatly from the mortality curve for New York covering the same period and including deaths from all causes (chart 22) Both curves may be regarded as measures of vitality, and they agree in indicating that vitality is higher

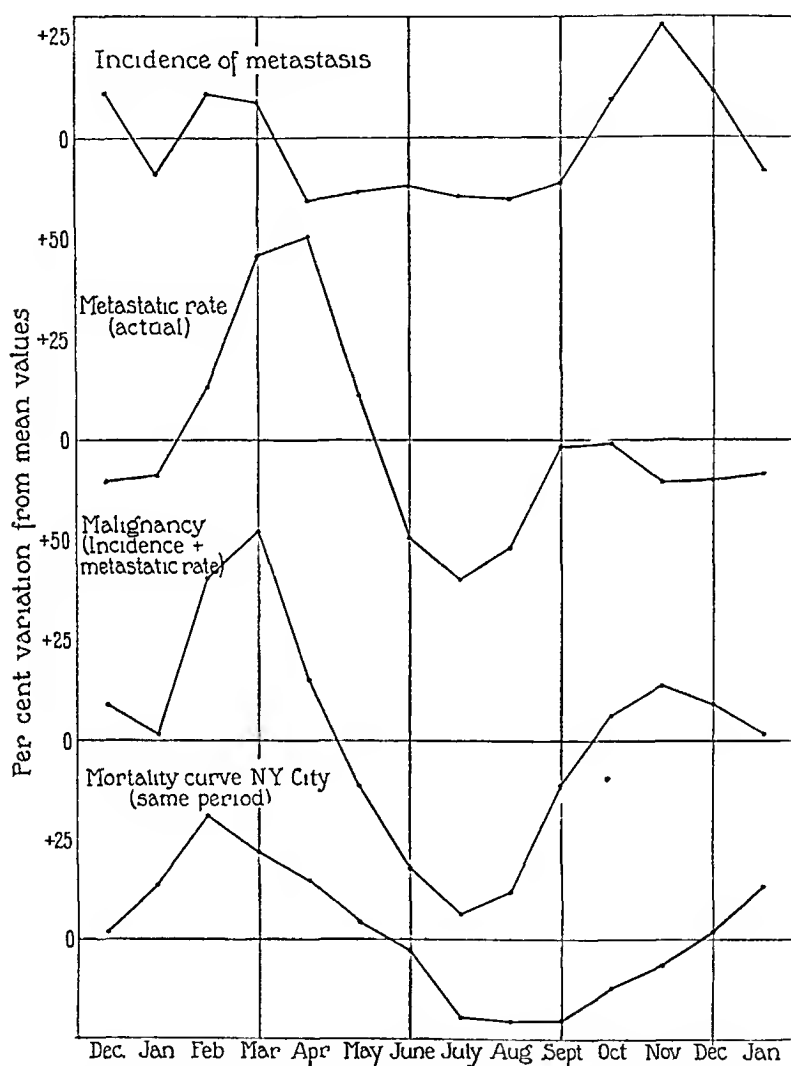


Chart 22—Susceptibility to a transplanted tumor Combined results for from 1922 to 1924

during summer than at other times This is precisely what would be expected if one assumes that vitality is a function of organic constitution, as may be seen by a comparison of the curves for organ balance and malignancy (chart 23) In some respects, the results given by actual values are even more striking than those shown by smoothed values

These two curves epitomize a situation which cannot be dismissed as mere coincidence—they present actual conditions. On the one hand, there are facts concerning the reaction of animals to inoculation of

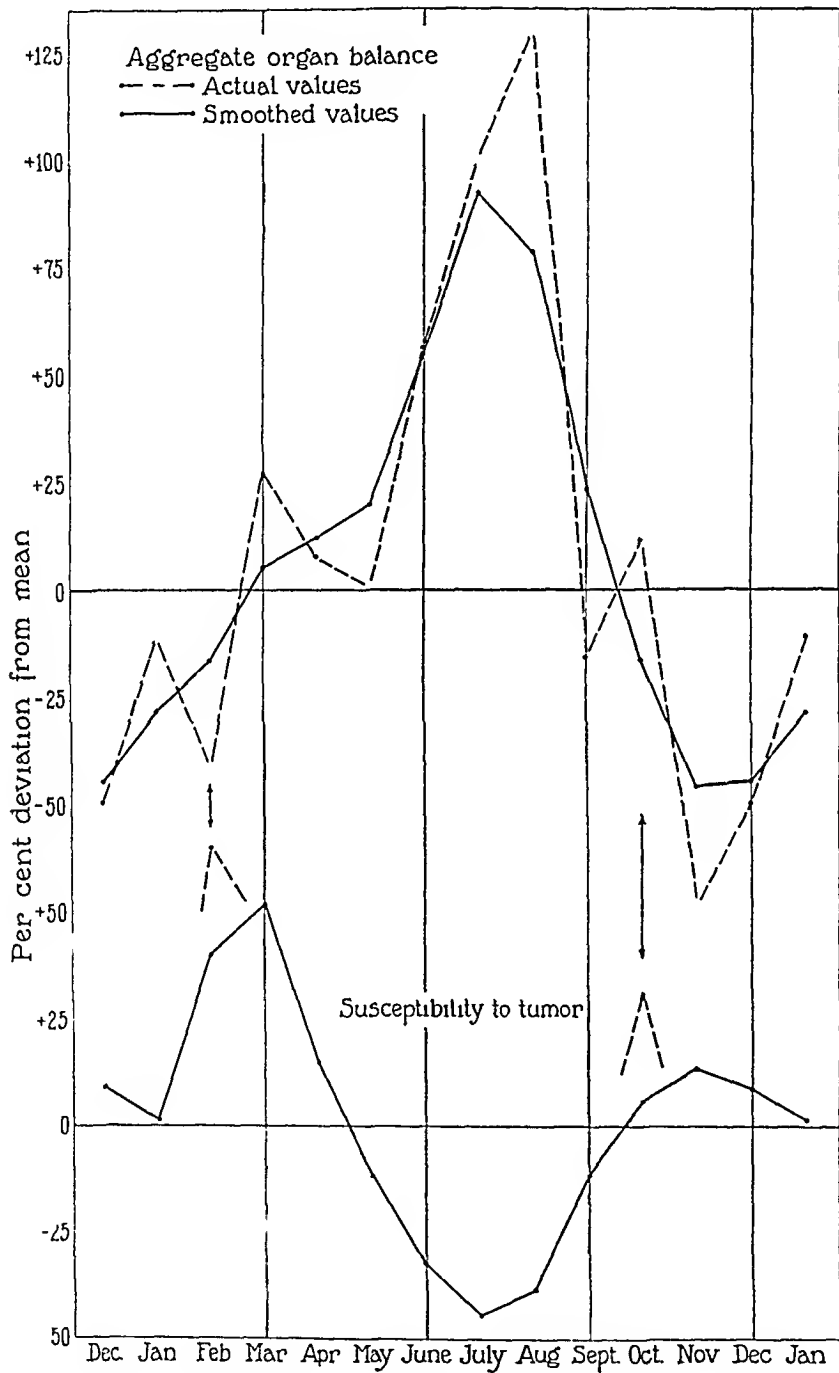


Chart 23—Organ balance and malignancy Concurrent determinations

tumor and, on the other, results for organic constitution based on animals taken from the same stocks. Our results for the reaction to syphilis are not so complete but as far as the critical periods are concerned they are in essential agreement.

So far, I have dealt with facts which could be ascertained by the use of simple methods of precision. I shall now consider the meaning of these facts. It has been found that organic constitution, chemical constitution and the reaction to disease are all variables which are distributed among an animal population in essentially the same manner, and that while the relative distribution of these characters within the group is virtually constant, the values for groups as a whole are subject to wide variation. It has also been found that constitution in its broadest sense and the reaction to disease show clearly defined seasonal variations of the same general order and that variations of a similar character can be produced experimentally by changing the mode of life of animals or by changes of environment. Furthermore, it has been found that disease gives rise to changes in physical and chemical constitution comparable with those that occur in normal animals at different periods of the year or with variations in susceptibility to disease and, conversely, that disturbance of the normal constitutional equilibrium gives rise to decided changes in the efficiency of the reaction to disease. It has also been found that the changes in physical and chemical constitution, metabolic activity and susceptibility to disease which are produced by environment are of the same nature as the differences presented by animals of different age groups, that is, the effects of environment and of age are expressed in a similar manner, so that the comparison of the ages of man with the seasons represents something more substantial than poetic fancy.

In brief, it would appear that in all these conditions one is dealing with two sets of factors, the one physical or chemical and the other functional, and that these factors are so intimately related that a variation in one is always reflected by a variation in the other. In other words, it seems that the reaction to disease is essentially a functional expression of a physicochemical status. According to this conception, the organs and tissues of the body are structural units which individually and collectively perform or control the functional activities of the body. The reaction to disease is as much a functional activity of the body as the processes of digestion and assimilation, and I know of no reason to regard the reaction to disease as more highly specialized than the performance of any other vital function.

The question now arises as to whether conditions that obtain among experimental animals throw any light on the relation of man to disease. The answer to this question is indicated by a comparison of the experimental results with the mortality curve for New York covering the same period. But, in attempting to apply the results of these experiments to human constitution and susceptibility to disease, differences in behavior are to be expected. Moreover, there are certain conditions that must be taken into account.

In the first place, a distinction must be drawn between a constitutional status as it affects general health and vitality and a status which is favorable or unfavorable for the development of a particular disease. While at present knowledge is limited to conditions which affect susceptibility as a general proposition or susceptibility to certain experimental diseases, there are definite indications of the manner in which specific susceptibilities may be affected. There are two phases of organic constitution to consider namely, the organ-body-weight relation or organ balance and the organ equilibrium or interrelation of organs. The basic relations of these states differ in persons by virtue of inheritance, they vary from month to month and from year to year in response to certain environmental influences. There is, however, a normal trend. In summer, the tendency is toward a high positive organ balance with a predominant endocrine influence, in winter, this condition is reversed, spring and fall are periods of transition. Moreover, the change from a summer to a winter status is accomplished, as a rule, by a rapid but continuous transition from the maximum level of July or August to a minimum level in November. The transition from winter to summer conditions, however, is irregular and discontinuous with a tendency to reverse movements, as a rule, the greatest irregularity occurs during February and March. This is merely an ebb and flow of a seasonal tide in the animal organism comparable with that in plants and subject to the influence of environmental conditions.

In estimating the bearing of these conditions on susceptibility, one must consider the form and level of constitutional values, the stability and the rate and smoothness of transition from one state to another. As I have already pointed out, high values are favorable and low values are unfavorable, but transition in either direction is a disturbing influence. This is particularly true of movements in a direction opposite to that of the normal trend. If the movement is gradual and continuous, incidence is affected more than the severity of the disease, but if the movement is rapid, irregular or extreme, the severity of the disease is increased accordingly. Thus, in the malignancy curve, the fall increase is due largely to an increase in the proportion of animals with malignant tumors, while the spring rise shows a greater increase in the distribution of metastases or in the actual malignancy of the tumor.

This phase of constitutional variation has a probable bearing on the seasonal prevalence of disease but, here again, a distinction must be drawn between acute and chronic diseases. I have worked entirely with chronic diseases, but in one case (tumor) the ultimate course of disease is usually determined within from two to four weeks after inoculation, while in the other (syphilis) the period is from two to three months. So far as the general trend of variations is concerned, the results for the two diseases agree, but, using the time of inoculation as the point

of reference, it has been found that susceptibility to the tumor was more closely related to prevailing constitutional and environmental conditions than susceptibility to syphilis, that is, the influence exerted at a particular time might be sufficient to determine the end-result in one case, whereas in the other, the time or length of action would be insufficient to produce a decisive effect, or the effect produced might be modified subsequently by the action of some other influence. The principle to be deduced is that the more acute the disease, the greater the influence of prevailing conditions and the greater the effect of abrupt or radical deviations from prevailing or normal conditions.

There is still another feature of this conception which should be made clear. In an effort to arrive at a few general principles, the results of these experiments have been condensed to the basis of a single year, while in reality they cover a period of several years. A comparison of results for different years shows that while variations in constitution and susceptibility tend to follow the same general trend from year to year, the time and extent of the variations may differ greatly. Moreover, there is some experimental evidence to show that constitutional variations and susceptibility to disease follow a cycle of progressive increase and decrease extending over a period of years. These observations may have a bearing on variations in the prevalence and severity of disease from year to year as well as the periodic recurrence of epidemics.

With reference to particular diseases, it is to be expected that conditions that are favorable for the occurrence of one disease may be unfavorable for the occurrence of another.<sup>4</sup> For, after all, pathogenic organisms must live and multiply in the body to produce disease. In this sense, the body is a culture medium, but all living things require appropriate conditions for their growth. Pathogenic organisms are not exceptions to this rule, and it will probably be found that the variations which occur in the chemical composition of tissues and fluids, independent of any specific immunologic reactions, are sufficient to account for wide variations in the prevalence and severity of particular diseases.

While I am not concerned, at this time, with the rôle of the causative agents of disease, attention may be called to the fact that if variations in dosage or virulence occurred in these experiments, they made no clearly defined impression on the results or else they followed the direction which I have ascribed to susceptibility and were subordinate to the influence of constitutional factors. This was to be expected since there are, after all, comparatively few infectious diseases which

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4 Sydenham. The Works of Thomas Sydenham, M.D. Translated from the Latin Edition of Dr. Greenhill by R. G. Latham. Printed for the Sydenham Society, London, 1848, vol. 1, ch. 2.

terminate fatally in more than 50 per cent of cases, that is, in most instances, the ultimate balance of power rests with the host and not with the infecting organism. Moreover, it is not impossible that some of the conditions which one is accustomed to regard as changes in virulence may be nothing more than expressions of growth in a favorable or unfavorable medium. In this case, virulence and susceptibility become one and the same thing—a function of constitution. But, in presenting the matter in this way, it is not my intention to minimize the importance of variations in the pathogenic properties of micro-organisms or to deny the occurrence of variations independent of the host. On the contrary, it has been found that so far as *T. pallidum* is concerned, not only are there differences in the pathogenic properties of different strains, but the properties of a given strain can be changed materially by experimental means, such as continued propagation under favorable or unfavorable conditions.

#### COMMENT

So far as they go, my experiments not only are in harmony with known facts concerning human constitution and susceptibility to disease but they enable one to state some of the general principles of the constitutional concept in simple terms of present knowledge and to visualize conditions which may influence susceptibility to disease. Constitution thus becomes a concrete reality which lends itself to measurement and test in accordance with the demands of modern science. The elementary conception of constitutional variation and its relation to disease which I have attempted to outline involves only one assumption, and that is that all functional activities of the body are either performed or controlled by organs and tissues and that the organs are provided in such numbers and amounts as are necessary for the performance of their appointed functions. One need not know the function of a single organ in order to show that persons differ from one another in respect of their organic equipment, or that they are persons and not standard machines or standard mediums for the growth of pathogenic micro-organisms. It can be shown that variations in the mass and mass relations of organs are constantly occurring in response to demands made by changing conditions of life and that these variations in organic constitution are accompanied by variations in chemical constitution, all of which may well be confined within the usual limits of normal, for they are normal. It can also be shown that these differences and variations in physical and chemical constitution are associated with differences and variations in functional activity and susceptibility to disease or in the degree of natural immunity.

Changing conditions of life affect individuals and groups, but as individuals differ in respect of their inherent constitutional equipment, they differ also in their reaction to influences of all kinds. Some are



capable of immediate and complete adjustment and others are slow to respond or are incapable of adjustment, so that when the members of a group are subjected to a change in the conditions of life or are exposed to infection under favorable or unfavorable conditions, the response obtained varies according to the capacities of the individual. Hence, even now, there is some understanding of how and why one person differs from another in respect of the general property of susceptibility to disease and why it is that the susceptibility of persons and of populations is not fixed but varies from time to time, independent of any immunity that may be acquired through previous exposure to a given disease.

When one is able to base all experiments on material of known genetic constitution and thus link together the two factors of heredity and environment, one will be in a position to gain a much clearer understanding of these intricate problems.

# THE PATHOLOGY OF THE PANCREAS IN NON-DIABETIC PERSONS

A STUDY OF ONE HUNDRED AND FIFTY-SIX CONSECUTIVE  
AUTOPSIES ON NONDIABETIC PATIENTS<sup>\*</sup>

SHIELDS WARREN, M D

BOSTON

In a recent article, Gibb and Logan<sup>1</sup> presented valuable data bearing particularly on pancreatic changes found at autopsy on 147 patients with diabetes mellitus. As their report was based on diabetic patients alone, it seems worth while to report the pathologic changes in a series of pancreases from nondiabetic patients.

The autopsies done on nondiabetic patients in this laboratory during 1928, a total of 156, form the basis of the present analysis. The anatomic causes of death range from acute conditions such as typhoid fever, pneumonia and postoperative pulmonary embolus to various chronic conditions, among which the late manifestations of carcinoma were frequent. Suffice it to say that only in rare cases were pancreatic changes an important factor in the clinical course or in the causation of death. The ages at death of these patients varied from 8 days to 87 years.

In all cases sections of the pancreas were studied after staining with eosin methylene blue (methylthionine chloride, U S P) and with phosphotungstic acid hematoxylin. In all autopsies done in less than three hours post mortem (this constituted a considerable portion of the autopsies), Mallory's aniline blue stain, Masson's three color stains and the granule stains of Bensley, Lane and Ukai were resorted to. The fixation was ordinarily Zenker's fluid, but frequently Helly's fluid, Champy's fluid and Regaud's method of fixation were utilized.

In table 1, the occurrence of interstitial pancreatitis and lipomatosis is given by decades. This is contrasted with table 1 A, which is table 1 of Gibb and Logan with their column headed "Arteriosclerosis" omitted.

The material is more concentrated in the older age groups. Not only do our nondiabetic cases show the same tendency for interstitial pancreatitis to increase in frequency with advancing age as do those of Gibb and Logan,<sup>1</sup> but also the frequency, while distinctly less, is never-

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<sup>\*</sup> Submitted for publication, May 25, 1929.

<sup>†</sup> From the Pathological Laboratory of the New England Deaconess Hospital and Palmer Memorial Hospital.

1 Gibb, W F, Jr, and Logan, V W. Diabetes Mellitus, A Study of One Hundred and Forty-Seven Autopsies, Arch Int Med **43** 376 (March) 1929.

theless so great as to preclude considering this a characteristic diabetic lesion. In making the diagnosis "interstitial pancreatitis" all cases showing only slight fibrosis were passed over, and only those showing clearcut (though at times focal) increase in interacinar or interlobular fibrous tissue included in the tabulation. In scattered instances, this fibrosis was accompanied by round cell infiltration. The occurrence of this fibrosis in nearly one half of the nondiabetic patients in the older age group rules it out as a characteristic diabetic lesion.

How far one may consider interacinar fibrosis as a cause of atrophy of the pancreatic tissue is open to question. I believe that in the pan-

TABLE 1—*Age Distribution According to Decades in Nondiabetic Patients*

Age	Cases	Interstitial Pancreatitis		Lipomatosis	
		Cases	Per Cent	Cases	Per Cent
0 to 10	3	0	0	0	0
11 to 20	2	0	0	0	0
21 to 30	3	0	0	0	0
31 to 40	4	1	25	0	0
41 to 50	31	3	9.6	6	19.3
51 to 60	46	16	34.7	13	28.2
61 to 80	66	32	48.4	17	25.7
81 to 90	1	1	100	1	100

TABLE 1 A (table 1 of Gibb and Logan)—*Age Distribution According to Decades in Patients with Diabetes*

Age	Cases	Interstitial Pancreatitis		Lipomatosis	
		Cases	Per Cent	Cases	Per Cent
10 to 20	12	1	8	0	0
21 to 30	15	4	26.6	0	0
31 to 40	16	7	44	1	6.3
41 to 50	36	23	64	8	22
51 to 60	45	29	64	20	44.4
61 to 80	23	15	65	12	52

creas, as in the liver, fibrosis is more frequently a result than a cause of injury to the parenchyma.

When lipomatosis is considered, there is some similarity of the data presented here to those of Gibb and Logan<sup>1</sup>. This change is absent in the younger age groups in both series. The occasional occurrence of extreme emaciation with depletion of almost all the stored fat of the body in cases of carcinoma has undoubtedly lowered the incidence of lipomatosis in my series. Whatever the mechanism of development of pancreatic lipomatosis may be in diabetic persons, in this series it is much more intimately related to the amount of body fat than to atrophy or fibrosis of the pancreas.

Even in the islands themselves the occurrence of abnormalities is not restricted to diabetes. Indeed, their occurrence in nondiabetic persons is a prerequisite if one considers insular changes the cause rather than the result of diabetes. Table 2 gives the frequency of lesions in the

islands and the occurrence of interstitial pancreatitis. With it is contrasted table 2 A (table 2 of Gibb and Logan<sup>1</sup>)

The preponderance of normal islands in this series is of course to be expected. Fibrosis of the islands may presumably be brought about by the same causes that produce interstitial fibrosis, and so the relatively high correlation of the two lesions in both series is to be expected.

The occurrence of hyaline islands in the pancreas of a nondiabetic patient was first pointed out by Ohlmacher,<sup>2</sup> and other cases have been reported in some detail by Cecil<sup>3</sup> and by Wright.<sup>4</sup> If one accepts hyaline degeneration of the islands as a cause rather than a result of diabetes, a

TABLE 2—*The Incidence of Lesions in the Islands*

	Cases	Interstitial Pancreatitis	
		Cases	Per Cent
Normal islands	130	40	30.7
Pyknotic islands	2	1	50
Slight fibrosis	7	6	85.7
Moderate fibrosis	1	3	75
Marked fibrosis	1	1	100
Hyaline islands	3	1	33.3
Hemachromatosis	0	0	0
Hydropic degeneration ((?))	2	0	0
Mitotic figures	2	0	0
Hemorrhage	1	0	0
Adenoma	2	0	0

TABLE 2 A (table 2 of Gibb and Logan) —*Effect of Interstitial Fibrosis on Island Cells*

	Cases	Interstitial Pancreatitis		Capsular Thickening	
		Cases	Per Cent	Cases	Per Cent
Normal islands	11	3	23	3	27
Pyknotic islands	15	7	46	3	20
Slight fibrosis	31	14	45	17	55
Moderate fibrosis	23	11	48	16	70
Marked fibrosis	25	16	64	16	64
Hyaline islands	30	22	73	16	58
Hemachromatosis	7	7	100	4	57

moderate number of cases must exist in which the lesion is not sufficiently marked to produce symptoms. In my series there are three such cases—1 per cent of the total number.

I have avoided the question of capsular thickening, as Gibb and Logan<sup>1</sup> did not state whether they had taken Otani's<sup>5</sup> type A as a norm

2 Ohlmacher, J. C. The Relation of the Islands of Langerhans to Diseases of the Liver, with Special Reference to Carbohydrate Metabolism, *Am J M Sc* **128** 287, 1904.

3 Cecil, R. L. Hyaline Degeneration of the Islands of Langerhans in Non-diabetic Conditions, *Am J M Sc* **147** 726, 1914.

4 Wright, E. W. Hyaline Degeneration of the Islands of Langerhans in Non-Diabetics, *Am J Path* **3** 461, 1927.

5 Otani, S. Studies on the Islands of Langerhans in the Human Pancreas, *Am J Path* **3** 1, 1927.

(the capsule made up of the basement membranes of surrounding acini) or the delicate, more or less complete connective tissue capsule frequently found about the islands

#### SUMMARY AND CONCLUSIONS

1 The pancreatic lesions in 156 autopsies on unselected nondiabetic patients are summarized

2 Practically any lesion found in the pancreas of diabetic patients can be duplicated in the pancreas of nondiabetic patients, though the frequency of occurrence of lesions of the islands is much less in the latter group

3 Interstitial pancreatitis occurs too frequently in nondiabetic patients to be considered a characteristic lesion of diabetes

4 In many cases lipomatosis is related to the amount of body fat

5 It is impossible from a study of the pancreas to diagnose the presence or absence of diabetes

# CALCIUM STUDIES

## IV THE CALCIUM CONTENT OF CEREBROSPINAL FLUID <sup>4</sup>

A CANTAROW, M D

PHILADELPHIA

The calcium content of human cerebrospinal fluid has not been extensively investigated, but the general impression is that it is extremely constant in health and in the great majority of pathologic states Halverson and Bergeim<sup>1</sup> and Pincus and Kramer<sup>2</sup> found the spinal fluid of human beings to average about 5 mg per hundred cubic centimeters Critchley and O'Flynn<sup>3</sup> found it to be 6.2 mg, practically constant at that figure and not varying characteristically in disease, with the exception of a fall in tetany and a rise in From's syndrome

The present study consists of the determination of the calcium content of the cerebrospinal fluid of 240 persons Sixty-eight may be classed as normal, the remaining 172 suffering with a variety of disorders which may be grouped under six headings (1) pulmonary tuberculosis in various stages of extent and activity, (2) disturbances of an atopic nature, including bronchial asthma, mucous colitis, vasomotor rhinitis and angioneurotic edema, (3) syphilis, including also paresis, tabes and cerebrospinal syphilis, (4) acute meningeal and cerebral infections, such as suppurative meningitis, tuberculous meningitis and epidemic encephalitis, (5) mental and neurologic disorders, including imbecility, mental deficiency, epilepsy, dementia praecox, mania and arteriosclerotic and alcoholic dementia, (6) a miscellaneous group including pregnancy and paroxysmal dyspnea of undetermined origin

### CALCIUM DETERMINATIONS

The calcium determinations were made by the Clark-Collip modification of the Kramer-Tisdall method<sup>4</sup> They are detailed in the accompanying table and may be summarized as follows

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Submitted for publication, June 15, 1929

From the Medical Service of Dr Thomas McCrae and the Department for Diseases of the Chest, Jefferson Hospital

1 Halverson, J O, and Bergeim, O The Calcium Content of Cerebrospinal Fluid, Particularly in Tabes Dorsalis, *J Biol Chem* **29** 337, 1917

2 Pincus, J B, and Kramer, B Comparative Study of the Concentration of Various Anions and Cations in Cerebrospinal Fluid and Serum, *J Biol Chem* **57** 463, 1923

3 Critchley, M, and O'Flynn, E The Calcium Content of the Cerebrospinal Fluid, *Brain* **47** 337, 1924

4 Clark, E P, and Collip, J B A Study of the Tisdall Method for the Determination of Blood Calcium with a Suggested Modification, *J Biol Chem* **63** 461, 1925

*Normal*—In sixty-eight essentially normal persons, the spinal fluid calcium varied from 4.52 to 5.50 mg per hundred cubic centimeters

*Pulmonary Tuberculosis*—For sixty-three patients with pulmonary tuberculosis of varying extent and activity, the figures ranged between 4 and 7.75 mg per hundred cubic centimeters. In none of these cases was tuberculous meningitis present. For thirty-six of this group the figures were within normal limits (from 4.5 to 5.5), for twenty-two they were above and for five, below normal.

*Calcium Content of Cerebrospinal Fluid in Sixty-Eight Normal Persons and in One Hundred and Seventy-Two Persons with Various Pathologic Conditions*

Condition	Cases	Calcium*	Normal†	Above†	Below†
Normal	68	4.52-5.50	68	0	0
Pulmonary tuberculosis	63	4.00-7.75	36	22	5
Bronchial asthma	25	4.39-6.33	8	16	1
Paresis	19	5.21-6.65	3	16	0
Tabes	12	5.23-6.29	3	9	0
Cerebrospinal syphilis	4	5.43-5.71	1	3	0
Acute meningitis	5	5.05-6.50	1	4	0
Tuberculous meningitis	3	5.88-7.50	0	3	0
Encephalitis	3	5.82-6.90	0	3	0
Epilepsy	4	5.00-6.00	3	1	0
Imbecility	2	4.90-5.30	2	0	0
Mental deficiency	2	5.60-5.80	0	2	0
Mania	1	5.85	0	1	0
Dementia praecox	3	5.82-6.73	0	3	0
Arteriosclerotic dementia	3	5.03-6.53	1	2	0
Alcoholic dementia	2	5.95-6.63	0	2	0
Syphilis	7	5.25-6.66	1	6	0
Pregnancy	6	4.50-5.25	6	0	0
Mucous colitis	3	5.62-6.00	0	3	0
Vasomotor rhinitis	2	5.75-6.10	0	2	0
Vasomotor ataxia	1	5.56	0	1	0
Paroxysmal dyspnea	1	5.00	1	0	0
Angioneurotic edema	1	5.50	1	0	0

\* Calcium values expressed in milligrams per hundred cubic centimeters

† Number of cases in each group within, above and below normal limits

*Atopic Disturbances*—In twenty-five patients suffering with bronchial asthma the concentration of spinal fluid calcium varied from 4.39 to 6.33 mg per hundred cubic centimeters. For eight of these the figures were within normal limits, for sixteen, above and for one, below normal.

Three patients with mucous colitis showed figures of from 5.62 to 6 mg of spinal fluid calcium, all being above normal.

For two patients with vasomotor rhinitis and one with angioneurotic edema the figures were from 5.5 to 6.1 mg, one being the high limit of normal and two above normal.

*Syphilis*—Seven patients with syphilis without demonstrable involvement of the central nervous system had concentrations of spinal fluid calcium of from 5.25 to 6.66 mg per hundred cubic centimeters. One was within normal limits and six above normal. In nineteen cases of paresis the figures ranged from 5.21 to 6.65 mg, being normal in three and above normal in sixteen. In twelve cases of tabes the figures were

from 5.23 to 6.29 mg, being normal in three and above normal in nine. Four patients with cerebrospinal syphilis had calcium concentrations of from 5.43 to 5.71 mg, one being normal and three above normal.

*Acute Local Infections*—The observations in the group with acute local infections were as follows. Five patients had meningococcus meningitis, with a spinal fluid calcium content of from 5.05 to 6.5 mg, for one of these, the figures were normal and for four, above normal. Three had tuberculous meningitis, with a calcium content of from 5.88 to 7.5 mg, all of these were above normal. Three had acute epidemic encephalitis and a calcium content ranging from 5.82 to 6.9 mg, all were above normal.

*Mental and Neurologic Disorders*—The group with mental and neurologic disorders includes four patients with epilepsy, two imbeciles, two with mental deficiency, one with mania, three with dementia praecox, three with arteriosclerotic dementia, and two with alcoholic dementia. The calcium values ranged from 4.9 to 6.73 mg per hundred cubic centimeters, six being within normal limits and eleven above normal.

*Miscellaneous*—In six cases of pregnancy of from three weeks to ten lunar months, the calcium values ranged from 4.5 to 5.25 mg, all within normal limits. One patient with paroxysmal dyspnea of undetermined origin had a calcium content in the spinal fluid of 5 mg, and one with vasomotor ataxia, 5.56 mg.

For sixty-seven of the 172 patients with a variety of disorders, the values for spinal fluid calcium were within normal limits, for ninety-nine they were above and for six below normal.

#### CONCLUSIONS

1 The calcium content of the cerebrospinal fluid of sixty-eight normal persons was found to be from 4.52 to 5.5 mg per hundred cubic centimeters. These figures support the prevalent belief in the constancy of the spinal fluid calcium under normal conditions.

2 The calcium content of the cerebrospinal fluid of 172 patients suffering with various disorders was from 4 to 7.75 mg per hundred cubic centimeters. If one considers the normal limits to be from 4.5 to 5.5 mg, sixty-seven of these were within normal limits, ninety-nine were above and six were below normal. There is evidently considerable variation in disease, the great majority of patients with inflammatory disease of the meninges and brain, those with atopic disorders and syphilis and many with pulmonary tuberculosis having concentrations of spinal fluid calcium well above the high limit of normal.



## CALCIUM STUDIES

### V THE RELATIONSHIP BETWEEN THE CALCIUM CONTENT OF CEREBROSPINAL FLUID AND BLOOD SERUM \*

A CANTAROW, M D

PHILADELPHIA

The growing interest in disturbances of calcium metabolism within recent years has stimulated investigation of the state of calcium in blood serum and its distribution in various body fluids. The cerebrospinal fluid has received particular attention since, if it is assumed that this fluid is a protein-free filtrate of blood plasma, its calcium content may be taken to represent the diffusible calcium of the blood.

The question arises as to whether the cerebrospinal fluid may be correctly regarded as a protein-free filtrate of blood plasma. The literature on this point has been extensively reviewed by Becht,<sup>1</sup> Weed,<sup>2</sup> and Levinson.<sup>3</sup> Several arguments have been advanced in support of the belief that the fluid is formed by a secretory process. Petit and Girard<sup>4</sup> demonstrated an increased flow following the administration of pilocarpine, muscarine and ether. Cappiletti<sup>5</sup> found a diminished flow following the use of atropine and hyoscyamine. Similar results have been obtained by many investigators and have been adduced as proof of the secretory origin of the fluid. Mott<sup>6</sup> believed that vacuoles which he found in the cells of the choroid plexus were conclusive evidence of secretory activity of these cells. Dixon and Halliburton<sup>7</sup> claimed a hormone action for extracts of the choroid plexus which, injected intravenously, resulted in an increased flow of cerebrospinal fluid.

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\* Submitted for publication, June 15, 1929

<sup>1</sup> From the Medical Service of Dr. Thomas McCrae and the Department for Diseases of the Chest, Jefferson Hospital

1 Becht, F. Studies on the Cerebrospinal Fluid, *Am J Physiol* **51** 1, 1920

2 Weed, L. H. The Cerebrospinal Fluid, *Physiol Rev* **2** 171, 1922

3 Levinson, A. Cerebrospinal Fluid, ed 2, St. Louis, C. V. Mosby Co., 1923, p. 51

4 Petit, L., and Girard, P. Sur la fonction secretoire et la morphologie de plexus choroides, *Arch d'anat. Micr* **5** 213, 1902-1903

5 Cappiletti, S. L'ecoulement du liquide cerebro-spinal par la fistula cephalo-rachidienne en conditions normales et sous l'influence de quelques medicamentes, *Arch. ital. de biol.* **36** 299, 1901

6 Mott, F. W. Oliver-Sharpey Lectures. Cerebrospinal Fluid, *Lancet* **2** 1, 1910

7 Dixon, W. E., and Halliburton, W. D. Cerebrospinal Fluid. I. Secretion of the Fluid. *J. Physiol.* **47** 215, 1913

On the other hand, Hassin<sup>8</sup> brought forward evidence to show that the function of the plexus is not secretion. Whether or not absorption occurs here, as he believes, there is no apparent reason why secreting cells should contain vacuoles. According to Becht,<sup>9</sup> the condition of the cells of the choroid plexus as described during the period of supposed "secretion" is the exact opposite of that seen in actively secreting cells. The latter have an inner granular and an outer clear zone, with distinct nuclei, whereas in the former there is an outer granular and an inner clear zone the nuclei being indistinct. Becht furthermore showed that all changes in spinal fluid outflow and pressure due to drugs can be traced to variations in intracranial venous and arterial tension, and concluded that there is no evidence that the fluid is formed by secretion. McClendon<sup>10</sup> on physicochemical grounds, claimed that the fluid is an ultrafiltrate of blood plasma. The differences in chemical determinations of plasma and spinal fluid may be due to differences in diffusibility of the various constituents of the blood and to a variation between the rates of entrance and absorption of certain elements of the fluid.

Levinson<sup>11</sup> found the hydrogen ion concentration of blood and spinal fluid to be identical and summed up the situation by this statement: "The fact that nearly all constituents of the blood are present in the cerebrospinal fluid and that their physicochemical properties are practically the same would make one believe that the cerebrospinal fluid is a direct product of the blood."

In view of these facts, there appears to be sufficient justification for considering the spinal fluid calcium to be the diffusible calcium of the blood. Furthermore, there seems to be a satisfactory agreement between the figures for spinal fluid calcium and those for diffusible serum calcium as determined by actual diffusion experiments. Halverson and Bergeim<sup>11</sup> and Pincus and Kramer<sup>12</sup> found the calcium content of human cerebrospinal fluid to average 5 mg. per hundred cubic centimeters, or from 45 to 50 per cent of the blood serum calcium. This ratio is the same as that reported by Neuhausen and Pincus<sup>13</sup> and by

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8 Hassin, G. B. Histopathology of Brain Abscess, *Arch. Neurol. & Psychiat.* **3** 616 (June) 1920.

9 Becht, F. Studies on the Cerebrospinal Fluid, *Am. J. Physiol.* **51** 1, 1920.

10 McClendon, J. F. The Formation and Composition of Cerebrospinal Fluid, *J. A. M. A.* **70** 977 (April 6) 1918.

11 Halverson, J. O., and Bergeim, O. The Calcium Content of Cerebrospinal Fluid, Particularly in *Tabs Dorsalis*, *J. Biol. Chem.* **29** 337, 1917.

12 Pincus, J. B., and Kramer, B. Comparative Study of the Concentration of Various Anions and Cations in Cerebrospinal Fluid and Serum, *J. Biol. Chem.* **57** 463, 1923.

13 Neuhausen, B. S., and Pincus, J. B. A Study of the Condition of Several Inorganic Constituents of Serum by Means of Ultrafiltration, *J. Biol. Chem.* **57** 99, 1923.

Updegraff, Greenberg and Clark<sup>14</sup> for diffusible calcium as determined by ultrafiltration experiments

# PRESENT INVESTIGATION

The present study consists of the determination of the calcium content of blood serum and cerebrospinal fluid withdrawn at the same time in each case from 199 different persons. Of these, sixty-eight were normal and 131 had various pathologic conditions. The spinal fluid calcium was considered the diffusible fraction of the serum calcium,

TABLE 1—*The Calcium Content of the Blood Serum and Cerebrospinal Fluid and the Nondiffusible Calcium in Sixty-Eight Normal Persons and in One Hundred and Thirty-One Patients with a Variety of Pathologic Conditions*

Condition	Cases	Blood Calcium Mg per 100 Cc	Diffusible Calcium	Nondiffusible Calcium	Diffusible Calcium*	Diffusible Calcium*	Nondiffusible Calcium*	Nondiffusible Calcium*
Normal	68	9.2-11.0	4.5-5.5	4.75-5.75				
Pulmonary tuberculosis	63	8.1-13.8	4.0-7.75	3.34-8.87	22	5	14	19
Asthma	25	7.0-12.67	4.39-6.33	1.5-7.5	16	1	2	18
Mucous colitis	3	9.84-11.0	5.62-6.00	4.22-5.00	3	0	0	2
Vasomotor rhinitis	2	10.55-10.7	5.75-6.10	4.45-5.00	1	0	0	1
Angioneurotic edema	1	8.2	5.5	2.7	0	0	0	1
Tetanus	6	9.83-12.25	5.23-6.21	4.62-6.04	5	0	1	2
Paralysis	5	9.87-13.16	5.21-5.98	4.59-7.21	4	0	2	2
Arteriosclerotic dementia	3	11.34-15.1	5.03-6.53	6.25-8.57	2	0	3	0
Dementia praecox	3	10.37-10.97	5.82-6.73	4.24-4.55	3	0	0	3
Alcoholic dementia	2	9.7-10.72	5.95-6.63	3.07-4.77	2	0	0	1
Mania	1	11.46	5.85	5.61	1	0	0	0
Epilepsy	1	10.15-11.2	5.0-6.0	4.15-6.0	1	0	0	1
Imbecility	2	9.23-9.6	4.9-5.3	3.95-4.7	0	0	0	2
Mental deficiency	2	10.3-11.5	5.6-5.8	4.7-5.7	2	0	0	1
Pregnancy	6	7.8-11.59	4.5-5.25	3.1-6.76	0	2	4	1
Vasomotor ataxia	1	9.6	5.66	4.04	1	0	0	1
Piroussimil dyspnea	2	8.2-11.0	3.8-5.0	4.4-6.0	0	1	1	1
Total (abnormal)	131	7.0-15.1	3.8-7.75	1.5-8.87	63	9	27	56

\* The last four columns represent the number of cases in each group with increased and decreased diffusible and nondiffusible calcium values.

the remainder of the serum calcium being nondiffusible. The method used for the determination of calcium was the Clark-Collip modification of the Kramer-Tisdall method for serum calcium.<sup>15</sup> The results are detailed in tables 1 and 2.

# COMMENT

The figures in the normal group are remarkably constant. The values for spinal fluid calcium coincide with those previously reported.

14 Updegraff, H., Greenberg, D. M., and Clark, G. W. A Study of the Distribution of the Diffusible and Nondiffusible Calcium in the Blood Sera of Normal Animals, *J. Biol. Chem.* **71**: 87, 1926.

15 Clark, E. P., and Collip, J. B. A Study of the Tisdall Method for the Determination of Blood Calcium with a Suggested Modification, *J. Biol. Chem.* **63**: 461, 1925.

for human beings by Halverson and Beigem<sup>11</sup> and Pincus and Kiamel,<sup>12</sup> although they are slightly above the figures obtained by Updegraff, Greenberg and Clark<sup>14</sup> by ultrafiltration. However, the ratio of spinal fluid to serum calcium, averaging 50 per cent, is in agreement with their figures for percentages of diffusible calcium. In twenty-one determinations on seventeen different normal persons, the latter investigators found that the variation in nondiffusible calcium was twice as great as that in the diffusible fraction. In this study, the normal values are at variance with this observation, the variation in both fractions being practically identical. In the abnormal group, however, the variation in nondiffusible calcium was approximately twice as great

TABLE 2—*The Ratio of Diffusible to Total Serum Calcium and to Nondiffusible Calcium*

Condition	Cases	Ratio D/T*	In creased D/T	De creased D/T	Ratio D/ND†	In creased D/ND	De creased D/ND
Normal	68	45.55			82.115		
Pulmonary tuberculosis	63	35.7-62.5	13	11	56.7-152	16	11
Asthma	27	40.8-80.0	17	2	68.9-400	19	2
Mucous colitis	3	54.5-59.1	2	0	120-133	3	0
Vasomotor rhinitis	2	53.5-57.8	1	0	115-137	1	0
Angioneurotic edema	1	67.1	1	0	203.7	1	0
Tabes	6	50.5-55.6	1	0	102-115	1	0
Paresis	5	45.2-55.3	1	0	82.5-124	2	0
Arteriosclerotic dementia	3	43.2-48.9	2	0	76.1-95.6	0	2
Dementia praecox	3	56.1-61.3	3	0	127-158	3	0
Alcoholic dementia	2	55.5-63.3	2	0	124-215	2	0
Mania	1	51.0	0	0	104	0	0
Epilepsy	4	45.4-59.0	1	0	83.3-144	1	0
Imbecility	2	51.0-57.2	1	0	101-134	1	0
Mental deficiency	2	50.4-54.0	0	0	101-119	1	0
Pregnancy	6	40.9-60.2	1	4	69.2-151	1	2
Vasomotor ataxia	1	57.9	1	0	137	1	0
Paroxysmal dyspnea	2	45.4-46.3	0	0	83.3-86.3	0	0
Total (abnormal)	131	35.7-80.0	47	19	56.7-400	53	17

\* Ratios expressed as percentage. D refers to diffusible calcium and T to total serum calcium.

† ND refers to nondiffusible calcium.

as in the diffusible. That this is not entirely due to a greater independent variability of the nondiffusible portion is evidenced by the fact that the total serum calcium variation appeared to be more directly proportional to that in diffusible than in nondiffusible calcium.

Changes in the calcium content of spinal fluid obviously may be due to alteration in one or both of two variable factors, namely, the diffusibility of the blood calcium, and the permeability of the cell membrane interposed between the blood stream and the subarachnoid system. Diseases of the brain, cord and meninges, particularly inflammatory and vascular disorders and conditions causing increased intracranial tension, tend to increase local permeability. This may be determined by the increased concentration in the spinal fluid of foreign substances such as dyes and biomides after their administration intravenously. It is also evidenced by the increased concentration of certain relatively poorly

diffusible constituents of the fluid, such as proteins and dextrose. The latter substance has been studied by many investigators. Crawford and I<sup>16</sup> found a condition of hyperglycorrhachia in various nervous and mental disorders. The decrease in spinal fluid sugar noted commonly in meningitis is due, not to decreased permeability but, in all probability, to the glycolytic action of the leukocytes or bacteria present in the fluid in these cases. Therefore, the spinal fluid calcium in the twenty-eight patients included in the group having nervous and psychiatric disorders in the present study cannot be accepted as representing a condition of calcium diffusibility existing throughout the tissues, but must be interpreted as being of purely local significance.

The maintenance of the life and activity of cells can be explained only on the basis of a physiologic variation in permeability of the cell membrane. Certain functional states, such as the contraction of muscle fibers, are known to be accompanied by increased permeability to electrolytes. Krogh and Harrop<sup>17</sup> have shown that there is a constant alteration in capillary permeability in response to the needs of the tissue, probably dependent on the local accumulation of carbon dioxide, lactic acid and other metabolic products. This fact is of importance in disease states. If a condition of general increased or decreased cellular permeability exists, the passage of various poorly diffusible substances should be correspondingly altered to some degree. Wells<sup>18</sup> expressed the belief that in nephritis a toxic effect is produced on all cells as well as capillaries, resulting in an increase in permeability. Petersen<sup>19</sup> found abnormal degrees of capillary permeability in various conditions, notably pulmonary tuberculosis. Manwaring,<sup>20</sup> as a result of his studies, concluded that increased cellular permeability will eventually be found to be the dominant fundamental factor in protein sensitization and anaphylaxis.

In the determination of diffusible calcium by artificial membrane methods, this factor of variable cellular permeability is entirely disregarded, while it is of importance to recognize any alteration in the distribution of calcium in the blood serum as indicated by its diffusibility through a membrane of constant permeability, it is perhaps more

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16 Crawford, B. L., and Cantarow, A. The Routine Examination of Cerebrospinal Fluid, *Am J M Sc* **171** 859, 1926

17 Krogh, A., and Harrop, G. A. Some Observations on Stasis and Edema, *J Physiol* **54** 125, 1920-1921

18 Wells, H. G. *Chemical Pathology*, ed 5, Philadelphia, W. B. Saunders Company, 1925, p. 387

19 Petersen, W. F. The Permeability of the Skin Capillaries in Various Clinical Conditions, *Arch Int Med* **39** 19 (Jan) 1927

20 Manwaring, W. H., Chilcote, R. C., and Hosepian, V. M. Capillary Permeability in Anaphylaxis, *J A M A* **80** 303 (Feb 3) 1923

important to know how much calcium has passed through the living membrane of variable permeability. This is particularly true in view of the important rôle that calcium plays in the regulation of cellular permeability. The ratio of diffusible to nondiffusible, or more correctly, of diffused to nondiffused calcium, is an expression of the distribution of calcium between the capillaries and tissues. The data presented here appear to be significant, indicating as they do some disturbance of a balance which is constant under normal circumstances. Any attempt to interpret these observations clinically would be beyond the province of the present discussion. However, it seems noteworthy that of the 103 patients suffering with disturbances other than those affecting the brain, cord and meninges, in only fifteen was the ratio of diffused to nondiffused calcium below normal, while in forty-two it was above normal limits. Still more significant is the fact that in a group of disorders probably representing an identical aberration of cellular function, as in the atopic patients, the observations are remarkably constant. Of the thirty-one subjects in this group only two showed a diminished ratio of diffused to nondiffused calcium, while twenty-four showed a distinct increase.

# THE EFFECT OF MECHANICAL CONSTRICTION OF THE HEPATIC VEINS

WITH SPECIAL REFERENCE TO THE COAGULATION OF BLOOD\*

W W BRANDES, M D

CHICAGO

In 1925, in the laboratory of the department of pathology of the Northwestern University Medical School, a method was devised for blocking the outflow of blood from the liver by mechanical constriction of the hepatic veins in the dog<sup>1</sup>. This procedure permits a temporary exclusion of the liver and splanchnic area from the general circulation and their return to it at will, and makes possible a study of some of the functions of the liver. It has advantages over the more drastic methods formerly employed of removing the liver entirely,<sup>2</sup> or permanently shutting it out of the circulation by an Eck fistula.<sup>3</sup> The trauma produced by mechanical constriction of the hepatic veins is less severe. It is, however, an acute experiment. It must be done under a general anesthetic, and observations must be made at short intervals during constriction, lasting from ten to forty-five minutes—that is, before the effects of trauma wear off entirely. In the experiment with an Eck fistula, the animal can be allowed to recover from trauma and the anesthetic can be dispensed with. In this procedure, however, the liver cannot be returned to the circulation, neither can this be done with complete removal. Furthermore, with the Eck fistula there is always a possibility of a partial or complete reestablishment of the circulation in the liver. The method of mechanically constricting the hepatic veins therefore merits consideration on the grounds that it is less severe and permits the study of the early changes that occur when the liver is removed from the circulation and those following the return to the circulation of the liver after temporary removal by the constriction.

## METHOD

\*The method of constricting the hepatic veins consists of making a midline abdominal incision about 4 inches (10.16 cm) in length

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\* Submitted for publication, May 24, 1929

\* From the Department of Pathology, Northwestern University Medical School

1 Simonds, J. P., and Brandes, W. W. Effect of Obstruction of the Hepatic Veins on the Systemic Circulation, *J. Physiol.* **72**: 320, 1925, Anaphylactic Shock and Mechanical Obstruction of the Hepatic Veins in the Dog, *J. Immunol.* **13**: 1, 1927

2 Mann, F. C. Studies in the Physiology of the Liver. Technic and General Effects of Removal, *Am. J. M. Sc.* **161**: 37, 1921

3 Schafer, E. A. Textbook of Physiology, Edinburgh, J. Pentland Young, 1898, vol. 1, p. 908. Stern, H. Beiträge zur Pathologie der Leber und des Icterus, *Arch. f. exper. Path. u. Pharmacol.* **19**: 39, 1885

Through this incision one end of a small-calibered rubber tube is passed through the foramen of Winslow. The two ends are then passed between the lobes of the liver and the parietal wall and diaphragm, over the ventral and anterior surface to the median fissure. To place the rubber tube in close proximity to the hepatic veins, it is passed through perforations made in the triangular ligaments when this can be done without hemorrhage. The two ends of the rubber tube are finally passed through two holes bored closely together in a small wooden block. To constrict the hepatic veins, traction is applied to the two ends of the rubber tube while, at the same time, the wooden block is pushed downward, the dog being in the supine position. The use of the block permits a more complete constriction of the hepatic veins and prevents great displacement or kinking of the inferior vena cava which would hinder the return circulation in that vessel.

#### EFFECT OF CONSTRICTION OF THE HEPATIC VEINS

The anatomic relationship of the hepatic veins varies somewhat in different animals. In some they are very short, emptying almost immediately into the inferior vena cava which makes complete constriction difficult without kinking the vena cava. In others they are longer and closely approximated, which is desired. In some dogs the ligaments extend to the free edge of the lobes of the liver and are narrow. This makes it difficult to perforate them without hemorrhage. Generally speaking, it was found that long, lean dogs that had been starved for twelve hours were best suited for this experiment.

All the experiments reported were performed with the animal under complete anesthesia. Ether was the anesthetic of choice because it gave greater relaxation.

Briefly stated, the changes<sup>4</sup> observed in the blood following constriction of the hepatic veins by the foregoing method for varying periods from ten to thirty minutes and the release of the constriction are as follows:

*Blood Pressure*—There is a precipitate fall in blood pressure (carotid artery) of from 40 to 60 mm of mercury. The pressure quickly reaches its lowest level and remains reasonably constant as long as the constriction is maintained. On release of the constriction the pressure rises to a level usually from 10 to 20 mm of mercury above its initial value. This occurs in from about ten to fifteen seconds. The rise is followed shortly by a decrease of about 20 mm, after which the pressure rises slightly and maintains a constant level at or

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<sup>4</sup> Simonds, J. P., and Brandes, W. W. Changes in the Blood Resulting from Mechanical Obstruction of the Hepatic Veins in the Dog, *Am J Physiol* 86: 623, 1928.



near the value of that before constriction Table 1 shows the average of the results from six dogs

Simultaneously with the fall in arterial pressure that in the portal vein rises quickly to about twice the original value, and falls precipitately when the obstruction is released and the arterial pressure rises

The percentage of fall in arterial pressure ranged from 26 to 42 It is not always possible to state that the obstruction to the hepatic veins is complete In the dogs in which the fall ranged from 37.5 to 42 per cent, further traction on the rubber tube failed to reduce the blood pressure to any greater extent It may be assumed, then, that complete obstruction to the hepatic veins will reduce the systemic blood pressure about 40 per cent This does not mean that complete obstruction of the hepatic veins will reduce the total volume of circulating blood only 40 per cent With the reduction in volume there is a compensatory vasoconstriction This is shown by the fact that during

TABLE 1—*Changes in Blood Pressure Resulting from Constriction*

Time of Observation	Blood Pressure Mm Hg
Before constriction	125
2 minutes after constriction	70
5 minutes after constriction	68
10 minutes after constriction	68
15 minutes after constriction	69
1 minute after release	140
5 minutes after release	130
10 minutes after release	125
15 minutes after release	125

occlusion of the hepatic veins, epinephrine injected intravenously is virtually without effect because the peripheral blood vessels are already constricted

The volume of the blood reaching the heart is one of the most important factors influencing blood pressure The marked fall in blood pressure during constriction of the hepatic veins is due to the reduction in the volume of blood reaching the heart The blood in the liver and splanchnic areas is prevented from returning to the heart Burton-Opitz<sup>5</sup> estimated that the equivalent of the total quantity of blood in the body passed through the liver every three minutes At any given moment there is a comparatively large volume of blood in this region which is greatly increased when the hepatic veins are constricted, since blood can still be forced into this area Impounding such a large volume of blood and preventing it from returning to the heart is the cause of the low arterial blood pressure

<sup>5</sup> Burton-Opitz, R The Vascularity of the Liver, *Quart J Exper Physiol* 3 300, 1910

That a compensatory vasoconstriction occurs in consequence of hemorrhage has been shown<sup>6</sup> In these experiments a vasoconstriction is also produced<sup>7</sup> The sharp rise in blood pressure after release of the hepatic veins is probably not due alone to the delivery of a greater volume of blood to the heart, but also to the fact that the heart now delivers a larger volume into a greatly reduced or constricted vascular bed

*Blood Concentration*—With the method of Lamson and Roca,<sup>8</sup> it was found that in most dogs there was a rapid decrease in the concentration of the blood during the first five minutes of constriction of the hepatic veins This was followed by a gradual recovery during the remainder of the period of constriction The method used is based on determinations of the percentage of hemoglobin, the sample of blood taken before constriction being used as the standard and its value

TABLE 2—*Changes in the Concentration of the Blood Resulting from Constriction*

Time of Observation	Blood Concentration per Cent
Before constriction	100.0
5 minutes after constriction	89.0
10 minutes after constriction	95.0
15 minutes after constriction	98.0
5 minutes after release	99.9
10 minutes after release	97.0
15 minutes after release	97.0
5 minutes after reconstriction	89.0
10 minutes after reconstriction	98.0
15 minutes after reconstriction	98.0
5 minutes after release	98.0

arbitrarily designated as 100 Although not free from criticism the method was considered sufficiently accurate to obtain comparative results in these experiments The average of results in six dogs at corresponding intervals of time is shown in table 2

The data in table 2 indicate that the blood becomes diluted rather quickly after mechanical constriction of the hepatic veins and then gradually increases in concentration The increase in the outflow of lymph from the thoracic duct is a probable factor in the dilution of the blood Fluid may enter from the tissues, as in low blood pressure, from hemorrhage, tending to restore the volume of blood<sup>9</sup> These two sources of fluid may account for the dilution of the blood during the first five or ten minutes after constriction The explanation for the gradual increase in concentration, while the constriction is still

6 Gesell, R Studies on the Submaxillary Gland IV A Comparison of the Effects of Hemorrhage and Tissue Abuse in Relation to Secondary Shock, *Am J Physiol* **47** 502, 1919

7 Simonds and Brandes (footnote 1, first reference)

8 Lamson, P D, and Roca, J The Liver as a Blood Concentration Organ, *J Pharmacol & Exper Therap* **17** 481, 1921

9 Guthrie, C C Observations in Shock, *Am J Physiol* **45** 544, 1918

applied, is not so simple. Three possible sources of red cells may be concerned. 1 After the first few minutes of constriction, the fluid from the thoracic duct contains some red blood cells. 2 A general vasoconstriction may force more cells into the circulating blood stream. 3 The increased pressure in the liver may force the constriction and deliver into the circulation a small amount of blood highly concentrated by loss of fluid which has escaped from the liver through the thoracic duct.

*Changes in the Liver* —With mechanical constriction of the hepatic veins there is a marked increase in the size of the liver. Its capsule becomes tense and its color much darker. Cut surfaces are very bloody. When the constriction is released and the blood pressure rises, there is a diminution in the size of the liver. Its capsule becomes less tense and the color less dark. These changes occur more slowly than do those following constriction.

TABLE 3—*Changes in the Volume of Blood Sugar Resulting from Constriction*

Time of Observation	Dextrose, Mg per 100 Cc of Blood
Before constriction	128
5 minutes after constriction	109
10 minutes after constriction	101
15 minutes after constriction	74
5 minutes after release	157
10 minutes after release	173
15 minutes after release	168
5 minutes after reconstriction	167
10 minutes after reconstriction	143
5 minutes after release	147
10 minutes after release	157

*The Flow of Lymph from the Thoracic Duct* —The flow of lymph from the thoracic duct, while the hepatic veins are constricted, shows an increase. The average increase in the number of drops for a series of six dogs was 5.2 times the number that escaped before and after constriction.<sup>10</sup> When the constriction is released there is a sharp decrease in the flow of lymph.

*Blood Sugar* —A surprisingly rapid fall in blood sugar follows constriction of the hepatic veins (method of Folin and Wu).<sup>11</sup> Table 3 shows the average of results in six dogs.

As soon as the constriction of the hepatic veins is released, the blood sugar promptly rises to a level considerably higher than that before the veins were mechanically constricted. In one animal it rose to 435 mg per hundred cubic centimeters of blood, the original level

10 Simonds, J. P., and Brandes, W. W. The Effect of Mechanical Obstruction of the Hepatic Veins upon the Outflow of Lymph from the Thoracic Duct, *J. Immunol.* **13** 11, 1927.

11 Folin, O., and Wu, H. A Simplified and Improved Method for the Determination of Sugar, *J. Biol. Chem.* **41** 367, 1920.

having been 163 mg. There was a slightly greater average fall in blood sugar in the first ten minutes following the first constriction (28 per cent) than in a similar interval after reconstriction (15 per cent). The average maximum fall in fifteen minutes after constriction was 42 per cent. This is considerably more than can be accounted for by dilution of the blood. Although it is not evident in table 3, the blood sugar not infrequently reaches a higher level after the second constriction than after the first.

The liver has been regarded as the organ that controls the blood sugar level, ever since Claude Bernard<sup>12</sup> found that blood from the hepatic veins constantly contained slightly more sugar than that in the portal vein, except during absorption of food. In 1857, he discovered glycogen and concluded that it was the chief source of carbohydrate material in the body. From it comes the dextrose of the blood. This theory was early upheld by Seegen<sup>13</sup> and most strenuously objected to by Pavy<sup>14</sup>. Later it was shown that removal of the liver or the shutting off of its blood supply in dogs<sup>15</sup> and in geese<sup>16</sup> was followed by either the disappearance or the marked diminution of the sugar of the blood. Recently it was shown that removal of the liver is followed by a progressive decrease in blood sugar with which symptoms develop that can be relieved by the administration of dextrose<sup>17</sup>. Hyperglycemia occurs after damage to the liver from poisoning with chloroform, hydrazine and phosphorus. The initial effect of these agents is a hyperglycemia<sup>18</sup>. Peptone injected intravenously produces changes in the blood sugar and gross changes in the liver strikingly similar to those obtained with mechanical constriction of the hepatic veins<sup>19</sup>. Ether anesthesia causes a slow, gradual rise in blood sugar<sup>20</sup>.

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12 Bernard, Claude. Nouvelle fonction, du foie, *Compt rend Acad d sc* **27** 249, 253 and 514, 1848

13 Seegen, J. Die Zuckerbildung im Thierkorper, *Arch f d ges Physiol* **50** 1, 1891, *ibid* **51** 396, 1891

14 Pavy, F. W. The Physiology of Carbohydrates, London, J. & A. Churchill, 1894

15 Tangl, F., and Vaughan, H. Beitrage zur Physiologie des Blutzuckers, *Arch f d ges Physiol* **61** 551, 1895. Schafer (footnote 3, p. 921)

16 Minkowski, O. Ueber die Folgen partieller Pankreasextirpation, *Arch. f exper Path u Pharmakol* **31** 85, 1893

17 Mann, F. C., and Magath, T. B. Blood Sugar Decrease Following Hepatectomy, *Arch Int Med* **30** 171 (July) 1922

18 Bodansky, M. The Production of Hypoglycemia in Experimental Derangements of the Liver, *Am J Physiol* **66** 375, 1923

19 Brandes, W. W., and Simonds, J. P. Changes in the Blood Sugar Following the Injections of Peptone in the Dog, *Am J Physiol* **86** 618, 1928

20 Epstein, A. A., and Aschner, P. W. The Effect of Surgical Procedures on the Blood Sugar Content, *J Biol Chem* **25** 151, 1917. Epstein, A. A., Reiss, I., and Branower, J. The Effect of Surgical Procedures on Blood Sugar and Renal Permeability, *ibid* **26** 25, 1918

Stimulation of a sensory nerve, interference with hepatic circulation or the administration of certain drugs results in hyperglycemia<sup>21</sup>

All the foregoing facts indicate that one of the early effects of stimulation or irritation of the liver is to cause its glycogen to be changed into dextrose, which is liberated into the blood stream. Obstruction of the hepatic veins causes a marked stasis in the liver, as evidenced by its gross changes. With this there is a local asphyxia and acidosis. Under the influence of these conditions, the glycogen present is changed into dextrose and the sugar of the blood in the liver becomes highly concentrated. The sugar in the general circulation is used up in metabolism and is not replaced as long as the blood from the liver is prevented from entering the general circulation. This will explain the decrease in blood sugar while the liver is shut out of the general circulation, and the marked increase after release, since the blood coming from the liver now is highly concentrated with dextrose. The agency converting glycogen into dextrose is believed to be the diastatic enzyme, glycogenase, which is present not only in the liver cell but also in the blood and lymph. That glycogen can exist in the liver cells in the presence of this powerful enzyme must be explained by the theory that its activities are held in check by inhibiting influences, which are under nervous or hormone control<sup>22</sup>. The action of glycogenase is extremely susceptible to changes in  $p^H$  for it has been shown that an increase in the hydrogen ion concentration of the blood flowing to the liver cells excites glycogenolysis<sup>23</sup>. That this, however, is the only factor in the process has been questioned<sup>24</sup>.

Changes in the hydrogen ion concentration are commonly observed in conditions in which there is also an increase in blood sugar. In severe hemorrhage a measurable increase in acidosis has been reported,<sup>25</sup> and hemorrhage increases the blood sugar<sup>26</sup>. Carbon monoxide given subcutaneously causes marked hyperglycemia,<sup>27</sup> and sodium bicarbonate, sodium carbonate and other alkalis have an inhibitory influence on the

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21 Brunings, W. Ein neuer Apparat für Blutorperchonzählung, *Arch f d ges Physiol* **96** 308, 1903

22 Macleod, J. J. R., and others. *Physiology and Biochemistry in Modern Medicine*, ed 5, St. Louis, C. V. Mosby Company, 1926, p. 888

23 Langfeldt, E. Blood Sugar Regulation and Origin of Hyperglycemia, *J Biol Chem* **46** 381 and 391, 1921

24 Tatum, A. L. Alkaline Reserve Capacity of Whole Blood and Carbohydrate Mobilization as Affected by Hemorrhages, *J Biol Chem* **41** 59, 1920

25 Crile, G. W. Studies in Exhaustion. V Hemorrhage, *Arch Surg* **7** 154 (July) 1923

26 Mulinos, M. G. Hemorrhage Hyperglycemia, *Am J Physiol* **86** 70, 1928

27 Mikami, Shago. Simultaneous Determinations of Blood Sugar Content and the Gas Content and Alkalinity of the Arterial Blood During Carbon Monoxide Poisoning, *Tohoku J Exper Med* **8** 237, 1926-1927

hyperglycemia of rabbits poisoned with carbon monoxide<sup>28</sup> In the hyperglycemia accompanying ether anesthesia there is also an increase in hydrogen ion concentration This increase is supposed to be dependent to a large extent on the production of lactic acid<sup>29</sup>

In the foregoing experiments colorimetric determinations of the  $p^H$  were made on the plasma The samples of blood were collected, under oil, from the jugular vein In all dogs there was a definite decrease in the  $p^H$ , ranging from 0.1 to 0.3, an average decrease of 0.2 The greatest changes were apparent after the constriction of the hepatic veins was released There was also a change in the hydrogen ion concentration associated with hyperglycemia

*Coagulation Time of the Blood*—During constriction of the hepatic veins the coagulation time of the blood was definitely decreased This was shown by Sabraze's capillary tube and Biffe's wire loop methods In the former, blood is drawn into capillary tubes, small portions are broken off at regular intervals until a strand of fibrin stretches across the gap This is taken as the end point In the latter method the wire loops are loaded with a film of blood, the loops are lowered into distilled water (38 C) at regular intervals When the blood does not diffuse out but remains solid in the loop, coagulation has taken place

With both these methods the normal coagulation time in these dogs varied between two minutes and thirty seconds, and four minutes and twenty seconds With such a short time for the normal, changes brought on by various procedures do not stand out so plainly The two methods gave favorable checks for comparative results in these experiments The average results in a series of dogs appear in table 4

In order to avoid the difficulties mentioned, the method of Hayem was employed in another series of experiments The jugular vein was exposed and covered with petrolatum Two cubic centimeters of blood was drawn from this vein into a syringe treated with petrolatum The blood was slowly run into a test tube  $\frac{3}{8}$  by 3 inches (0.9 by 7.6 cm) This was placed in a water bath at 38 C The tube was tilted every fifteen or thirty seconds until it could be inverted without spilling the contents This was taken as the end-point With this method, several points in technic<sup>30</sup> were carefully observed (a) The temperature was kept constant, (b) the method of obtaining the samples was uniform, (c) the amount of foreign contact was the same in each sample, and

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28 McDonell, L., and Underhill, F. P. Studies on Carbohydrate Metabolism XIV Influence of Alkali Administration upon Blood Sugar Content in Relation to the Acid-Base Producing Properties of the Diet, *J Biol Chem* **29** 227, 1917

29 Ronzoni, E., Koechig, I., and Eaton, E. P. Rôle of Lactic Acid in the Acidosis of Ether Anesthesia, *J Biol Chem* **61** 465, 1924

30 Addis, T. The Coagulation of Blood (Time) in Man, *Quart J Exper Physiol* **1** 305, 1908

(d) the end-point was sharp and indicated approximately the same degree of coagulation. Special care was taken to avoid injury to the tissues when the sample was drawn in order to prevent the admixture of tissue juice with the drawn blood. The average results obtained with this method are shown in table 5.

The percentage of error in Hayem's method, as applied in these experiments, was determined to be about 10.

From table 5 it is evident that there is a decrease in the coagulation time of the blood within fifteen minutes after constriction of the hepatic veins. With the first methods this was about 50 per cent, with the latter about 25.4 per cent.

TABLE 4—*Changes in Coagulation Time Resulting from Constriction, Tested by Sabrazé's Capillary Tube and Biffé's Winc Methods*

Time of Observation	Coagulation Time, Seconds
Before constriction	206
5 minutes after constriction	127
10 minutes after constriction	93
15 minutes after constriction	93
5 minutes after release	139
10 minutes after release	149
15 minutes after release	159
5 minutes after reconstriction	103
10 minutes after reconstriction	91
5 minutes after release	135

TABLE 5—*Changes in Coagulation Time, According to Method of Hayem*

Time of Observation	Coagulation Time	
	Minutes	Seconds
Before constriction	12	40
5 minutes after constriction	11	20
10 minutes after constriction	10	30
15 minutes after constriction	9	15
5 minutes after release	10	50
10 minutes after release	12	10
15 minutes after release	13	0

An effort was made to determine what other changes might have occurred in the blood following constriction of the hepatic veins to account for this decrease in the coagulation time.

**Blood Fibrin.** Determinations of blood fibrinogen were made according to the gravimetric method of Foster and Whipple<sup>31</sup>. The fibrin was precipitated by recalcifying oxalated plasma. It was found that 1 cc of a 1 per cent solution of sodium oxalate did not prevent coagulation of all the samples drawn after the hepatic veins had been constricted. One cubic centimeter of a 2 per cent solution was then used as the anticoagu-

31 Foster, D. P., and Whipple, G. H. An Accurate Method for the Quantitative Analysis of Blood Fibrin in Small Amounts, *Am J Physiol* **22** 58, 1921.

lant The fibrin values, expressed in milligrams per hundred cubic centimeters of blood, were calculated by Gram's formula <sup>32</sup>

*Total oxalated blood—total volume cells fibrin in 2 cc oxalated plasma, 100*—Total oxalated blood—volume oxalate solution  $\times$  2 equals milligrams of fibrin in 100 cc of blood The average of results obtained in a series of six dogs is shown in table 6

There is a decrease of slightly over 10 per cent in fibrinogen after the hepatic veins are constricted The decrease is no greater than what can be accounted for by dilution of the blood The release after constriction of fifteen minutes or more is followed by a definite increase (21 per cent) in fibrinogen value

Various organs have been considered as the site of the formation of fibrinogen Brown-Séquard,<sup>33</sup> Dastre,<sup>34</sup> Matthews<sup>35</sup> and others concluded that it was formed in the intestines Doyon and Gautier<sup>36</sup> decided that the intestines, while not essential to its production, contributed to its formation The lungs and skin<sup>34</sup> have been considered as its seat of origin The decreased coagulability of the blood in phosphorus<sup>37</sup> and chloroform<sup>38</sup> poisoning has been shown to be due to the disappearance of

TABLE 6—*Determinations of Blood Fibrinogen Before and After Constriction*

Time of Observation	Mg, per 100 Cc
Before constriction	280
10 to 15 minutes after constriction	250
5 minutes after constriction	340

fibrinogen In animals with an Eck fistula the fibrinogen in the blood was found to disappear rapidly and there was no regeneration <sup>39</sup> Total

32 Gram, H C A New Method for the Determination of Fibrin Percentage in Blood and Plasma, J Biol Chem **49** 279, 1921

33 Brown-Séquard, E Sur des faits que semblent montrer que plusieurs kilogrammes de fibrine se forment et se transforment, chaque jour, dans le corps de l'homme, et sur le siege de cette production et de cette transformation, J de physiol et de path gen **1** 298, 1858

34 Dastre, A Contribution a l'étude de l'évolution du fibrinogène dans le sang, Arch de Physiol **5** 327, 1893

35 Matthews, A The Origin of Fibrinogen, Am J Physiol **3** 53, 1899

36 Doyon, M, and Gautier, C Sur le rôle de l'intestine dans la fibrinogenèse, J de physiol et de path gen **9** 405, 1907

37 Corin, G, and Ansiaux, G Untersuchungen uber Phosphorvergiftung, Vrtljschr f gerichtl Med **7** 80, 1894 Jacoby, M Ueber die Beziehungen der Leber und Blutveränderungen bei Phosphorvergiftung zur Autolyse, Ztschr f Physiol Chem **30** 174, 1906

38 Doyon, M Incoagulabilité du sang provoquée par le chloroforme, rôle du foie, Compt rend Soc de biol **58** 30, 1905 Whipple, G H, and Hurwitz, S H Fibrinogen of the Blood as Influenced by Liver Necrosis of Chloroform Poisoning, J Exper Med **8** 136, 1911

39 Meek, W J Relation of the Liver to the Fibrinogen Content of the Blood, Am J Physiol **30** 161, 1912



removal of the liver causes a progressive decrease in fibrinogen<sup>40</sup> Diseases of the liver in which there is destruction of parenchyma are associated with decrease in fibrogen<sup>41</sup> The evidence from the literature that fibrinogen is formed solely in the liver is, thus, quite convincing In the present experiments performed the increase in fibrinogen after release of the hepatic veins can be assumed to be due to a stimulation of the liver by the stasis, to increased formation of fibrinogen, or to the accumulation in the hepatic blood of fibrinogen formed at a normal rate In either case an excess is set free in the blood after the constriction is released The decrease during constriction was slight and can be explained on the basis of dilution alone The change in coagulation time cannot be satisfactorily explained on the basis of the fibrinogen factor, at least not on the changes in quantity of this element

The theory has been advanced that blood proteins constitute merely a continuous series of disintegration products of tissue proteins, of which the first step is the least dispersed of the blood proteins, fibrinogen<sup>42</sup> This theory accounts well for the increase in fibrinogen content with injury to the tissues Applying it to the foregoing observations, one would expect a heightened coagulability of the blood when blood which had stagnated in the liver and splanchnic regions was returned to the circulation

**Blood Platelets** Blood platelet counts were made before and after constriction and release of the hepatic veins, by the method of Spitz<sup>43</sup>

The averages of results are given in table 7

The platelets during constriction of the hepatic veins show a decrease of about 24 per cent A decrease in these elements would be expected as a result of dilution of blood following the sudden withdrawal of such a large volume of blood from the general circulation The table shows but a slight increase in number of platelets after release of the constriction If the blood impounded in the liver contained the normal number of these elements, a greater rise, perhaps, might be expected after releasing this blood Many of the platelets in this area probably disintegrate during the period of constriction as a result of stasis Changes in the  $p^H$  may also be factors in their disintegration

It is as yet unsettled just what part the platelets play in the process of coagulation In thrombosis it has often been observed that fibrin is

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40 McMaster, P. D., and Drury, D. R. The Source of Fibrinogen, *Proc Soc Exper Biol & Med* **26** 490, 1929

41 Isaac-Krieger, K., and Hiege, A. Der Fibrinogengehalt des Blutes bei Leberkrankungen, *Klin Wchnschr* **2** 1067, 1923

42 Hertzfield and Klinger. *Biochem Ztschr* **83** 43, 1917, cited by Wells, H. G. *Chemical Pathology*, ed 5, Philadelphia, W. B. Saunders Company, 1925, p. 350 Starlinger, W., and Frisch, A. Chemisch-Physikalische Blutuntersuchungen zur Frage der Protoplasmaaktivierung, *Ztschr f d ges exper Med* **24** 143, 1921

43 Thomsen, O., cited by Reiman, H. A. The Blood Platelets in Pneumococcus Infection, *J Exper Med* **40** 553, 1924

first formed about masses of platelets clinging to the wall of the vessel. This indicates that they take part in the process. Howell<sup>44</sup> and others stated their belief that they give rise to thromboplastic substances, cephalin which neutralizes antithrombin. They are considered more important than the leukocytes in producing substances that participate in the coagulating mechanism.<sup>45</sup> It is also stated that platelet counts below 100,000 in the human being are generally accompanied by a tendency to bleed.<sup>46</sup> Tait and Green<sup>47</sup> stated that the thrombocytes of the frog are essential to the initiation of the clotting mechanism. Tait and Burke<sup>48</sup> observed that deplateletized mammalian blood does not clot on contact with foreign matter. They concluded that platelets are essential to the process. Mills<sup>49</sup> showed that platelets contain tissue fibrinogen.

The results of the experiments reported do not give definite evidence of the rôle of platelets in the process of coagulation. There is a decrease in number during constriction of the hepatic veins that is also associated with a decrease in coagulation time. This decrease in platelets, however, is not marked, and there is no evidence that it is due to disintegration of

TABLE 7—*Blood Platelet Counts Before and After Constriction of the Hepatic Veins*

Time of Observation		Platelets per Cu. Mm
Before constriction		292,800
10 to 15 minutes after constriction		220,320
10 to 15 minutes after release		235,400

platelets in the general circulation. It seems more probable that it is due to marked changes in the volume of blood.

It was frequently noted that the coagulation time taken immediately after release of the constriction of the hepatic veins was noticeably shortened beyond what it was during constriction. The platelets increased only slightly on release. It may be assumed that platelets disintegrated in the area of blood stasis. After release of the constriction there is also an increase in fibrin. These factors would tend to increase the

44 Howell, W. H. *Textbook of Physiology*, ed. 10, Philadelphia, W. B. Saunders Company, 1927, p. 468.

45 Bordet, J., and Delange, L. *La coagulation du sang et la genese de la thrombine*, Ann. de l'inst. Pasteur **26** 657, 1912, Bull. Johns Hopkins Hosp. **32** 213, 1921.

46 Gram, H. C. *On the Platelet Count and Bleeding Time in Diseases of the Blood*, Arch. Int. Med. **25** 325 (March) 1920.

47 Tait, J., and Green, F. *The Spindle Cell in Relation to Coagulation of the Frog's Blood*, Quart. J. Exper. Physiol. **16** 141, 1926.

48 Tait, J., and Burke, H. E. *Platelets and Blood Coagulation*, Quart. J. Exper. Physiol. **16** 129, 1926.

49 Mills, C. A. *The Role of the Platelets on Blood Clotting*, Chinese J. Physiol. **1** 235, 1925.

coagulability This tendency is shortly replaced by prolongation of the coagulation time

Blood Calcium Ionized calcium (Sabbatini) is essential to coagulation, since blood from which calcium has been precipitated does not clot The mechanism of its action has not been agreed on Pekelharing, Harmmarsten and Morawitz <sup>50</sup> thought it necessary for the transformation of prothrombin into thrombin Howell <sup>51</sup> expressed the belief that calcium activates prothrombin whenever it is not inhibited by antithrombin

In the foregoing experiments, the method of Kramer and Tisdall <sup>52</sup> being used for the determination of blood calcium, the results were as given in table 8

These results show that there is a decrease of about 15 per cent in the calcium of the blood during constriction This parallels the change in the concentration of the blood and can be explained on a basis of dilution of the blood Hence, changes in this factor can hardly be considered sufficient to account for the changes in coagulability of the blood

TABLE 8—*Determinations of Blood Calcium Before and After Constriction*

Time of Observation	Mg, per 100 Cc of Blood
Before constriction	10.5
10 to 15 minutes after constriction	8.8
10 to 15 minutes after release	9.0

In order to determine the effect of dilution on the coagulation time, 0.85 per cent sodium chloride solution was injected intravenously in quantities sufficient to dilute the blood from 10 to 30 per cent Before injection the coagulation time averaged eleven minutes and ten seconds, from five to ten minutes after, it averaged ten minutes and fifty seconds Mere dilution, therefore, causes practically no change in the coagulation time In animals that were first bled from 50 to 100 cc and then were given an injection of an equal volume of physiologic solution of sodium chloride there was a decrease in coagulation time of 26 per cent within ten minutes By this procedure a marked dilution of the blood was produced, but there was also the added feature of hemorrhage

Clamping of the inferior vena cava above the entrance of the level of the renal veins caused practically no change in coagulation time during the first five minutes After ten minutes a slight decrease, an average of 11 per cent, was noted This decrease is small and can be considered

<sup>50</sup> Pekelharing, Harmmarsten and Morawitz, cited by Wells Chemical Pathology, p 352

<sup>51</sup> Howell (footnote 44, p 466)

<sup>52</sup> Kramer, B, and Tisdall, F F Method of Determining Blood Calcium, J Biol Chem 47 475, 1921, ibid 48 233, 1921

within the range of experimental error. Clamping of the inferior vena cava at the aforesaid level removes a large volume of blood from the circulation. While this does not equal the volume withheld when the hepatic veins are occluded, these experiments indicate that the mere removal of a volume of blood from the circulation is not the only factor in decreasing the coagulation time under the conditions of these experiments.

In a limited number of animals the  $p''$  of the blood from the jugular vein was determined. In each case there was a definite decrease. Further work, however, is being carried out on this and on the carbon dioxide, prothrombin and antithrombin factors.<sup>53</sup>

#### COMMENT

Several factors suggest themselves as possibly concerned in the definite decrease in coagulation time during mechanical constriction of the hepatic veins.

1 The effect of trauma may be considered. It is believed by some writers that trauma in itself does not affect the coagulation time.<sup>53</sup> In the experiments cited, this was shown not to be the only factor, in the following way. The animals were anesthetized and, after all operative trauma had been committed, the coagulation time was allowed to become stabilized during the following thirty or sixty minutes. Constriction of the hepatic veins at this time caused a definite decrease in coagulation time. It is evident, therefore, that constriction alone causes a change.

2 Coagulation time is gradually shortened during ether anesthesia.<sup>53</sup> This is said to occur within the first fifteen minutes after induction and is believed to be the result of an outpouring of epinephrine.<sup>54</sup> The liver is regarded as essential to the action of epinephrine in increasing coagulability of the blood. It is stimulated by this agent to increased production of prothrombin.<sup>55</sup> A possible excess of epinephrine will not explain the decreased coagulation time in these experiments because the liver was excluded from the circulation. Hemorrhage has been reported to cause an increased output of epinephrine. After suprarenalectomy, however, hemorrhage will decrease the coagulation time,<sup>56</sup> and double adrenalectomy

53 Rabinovich, M. Coagulation Time of the Blood During Anesthesia, *Brit J Exper Path* **8** 343, 1927.

54 Cannon, W. B. The Emergency Function of the Adrenal Medulla in Pain and the Major Emotions, *Am J Physiol* **33** 357, 1913. Cannon, W. B., and Mendelhall, W. L. Pain and Emotional Disturbances of Coagulation Time, *Am J Physiol* **34** 251, 1914.

55 Grahfield, G. P. Factors Affecting the Coagulation Time of the Blood. IX. The Effect of Adrenin on the Factors of Coagulation, *Am J Physiol* **42** 46, 1917.

56 Hirochi, Tachi. Simultaneous Determinations of the Epinephrine Liberation and the Sugar Content and the Coagulation Time of the Blood in Non-Anesthetized, Non-Fasted Dogs After Hemorrhage, *Tohoku J Exper Med* **11** 205, 1928.

tomy in cats has been found progressively to decrease the coagulation time <sup>57</sup>

3 Changes in the concentration of blood sugar are frequently found associated with changes in the coagulation time of the blood. It has been thought that this might be a possible cause, indirectly, by stimulating the liver to the production of more fibrinogen <sup>58</sup>. Cannon, however, showed that injection of sugar alone has no effect on coagulation time. In the foregoing experiments also the decrease in coagulation time occurred during constriction when there was a definite hypoglycemia, and increased after release of constriction of the hepatic veins when the blood sugar level was at its highest point.

4 Changes in the concentration of the blood may cause changes in the coagulation time. When blood becomes more dilute the bodies concerned in coagulation are also diluted, which should cause an increase in coagulation time unless there is an excess of coagulating factors in the blood or unless dilution affects those bodies which inhibit coagulation more than it affects those which cause clotting. If this is the case a considerable degree of dilution may occur before there is a noticeable effect on coagulation, or dilution of anticoagulant factors may even shorten the coagulation time. The greatest dilution occurred shortly after the hepatic veins were constricted. The coagulation time became shorter at the same time or slightly later. It is possible that lymph from the thoracic duct, which is greatly increased during constriction, may carry coagulating factors to the blood. A definite impression was gained that lymph collected during the period of constriction clotted with greater rapidity and more firmly than that collected before constriction. Dilution of the blood, and, thus, of the factors concerned in coagulation by the intravenous injection of a volume of physiologic solution of sodium chloride equal to 30 per cent of the total volume of the blood, caused practically no change in coagulation time.

5 Conditions that cause changes in coagulation are also associated with changes in  $p^H$ . In ether anesthesia there is a definite decrease in  $p^H$  as well as a decrease of the coagulation time of the blood <sup>59</sup>. The carbon dioxide capacity of the plasma decreased 36.9 per cent in two hours of ether anesthesia <sup>60</sup>. The injection of a weak acid into dogs caused a

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57 Barlow, O. W., and Ellis, M. M. Effect of Double Adrenalectomy on the Coagulation Time in Cats, *Am J Physiol* **70** 58, 1924.

58 Partoo, A., and Svec, F. Gesetzmässiger Zusammenhang zwischen Blutzucker Gehalt und Blut, *Deutsche med Wchnschr* **53** 1857, 1927.

59 Van Slyke, D. D., Austin, J. H., and Cullen, G. E. The Effect of Ether Anesthesia on the Acid-Base Balance of the Blood, *J Biol Chem* **53** 277, 1922.

60 Atkinson, H. V., and Ets, H. N. Chemical Changes of the Blood Under the Influence of Drugs, *J Biol Chem* **52** 5, 1922.

reduction of the alkali reserve to a low level. At the same time there was a shortening of coagulation time<sup>61</sup>. Injection of an alkaline solution of the same strength, after the acid had been injected, caused a rise in alkali reserve and a lengthening of the coagulation time. Fibrinogen, the precursor of fibrin which is the basic element of a blood clot, is present in the plasma as a dispersed colloid. In the process of clotting, fibrinogen (hydrosol) is changed into fibrin (hydrogel). Electrometric fibrination has determined the iso-electric point of fibrin to be  $p^H$  5.5<sup>62</sup>. The iso-electric point of blood, that is, the hydrogen ion concentration at which blood coagulates, is about  $p^H$  4.6<sup>63</sup>. Clotting of rabbit's plasma has been found to be accompanied by a sudden but slight diminution of its alkalinity<sup>64</sup>.

In the experiments described there was a definite decrease in the  $p^H$  and alkali reserve during constriction of the hepatic veins. It is not known whether variations in  $p^H$  affect coagulating factors more than anticoagulating factors. In the foregoing experiments, however, the coagulation time increased after release of the hepatic veins, the period when the  $p^H$  was lowest. This suggests that possibly there was present in the blood an anticoagulant factor of hepatic origin either formed by the liver or produced as a result of possible injury to the liver. This would be in harmony with the theory of Howell<sup>65</sup>. There is no satisfactory method for a quantitative determination of heparin in the blood and, considering that it has proved to be a carbohydrate body and probably a glycuronic acid, there is little probability that a method of this kind can be devised<sup>66</sup>. It may be argued that antithrombin is present in the blood and in fifteen minutes' time does not change sufficiently to cause alterations in coagulation time. The anticoagulant action of heparin, however, has been shown to wear off rapidly *in vitro*<sup>67</sup> and when injected into dogs<sup>68</sup>.

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61 Mills, C. A. The Action of Tissue Extracts in the Coagulation of the Blood, *J. Biol. Chem.* **46** 167, 1920.

62 Nordbo, R. Zur physikalischen Chemie des Fibrinogen, *Biochem. Ztschr.* **191** 150, 1927.

63 Alexander, J. *Colloid Chemistry, Theoretical and Applied*, New York, Chemical Catalog Company, 1928, vol. 2, p. 425.

64 Hirsch, E. F. Changes in Hydrogen Ion Concentration of the Blood with Coagulation, *J. Biol. Chem.* **61** 795, 1924.

65 Howell, W. H. Two New Factors in Blood Coagulation. Heparin and Pro-Antithrombin, *Am. J. Physiol.* **47** 328, 1917, The Purification of Heparin and Its Presence in Blood, *ibid.* **71** 553, 1925.

66 Howell, W. H. Personal communication to the author.

67 Gross, P. Duration of Anticoagulant Action on Heparin *in Vivo* in Relation to Dosage, *Proc. Soc. Exper. Biol. & Med.* **26** 383, 1929.

68 Shionoya, Takuji. Studies in Experimental Extra-Corporeal Thrombosis. III. Effects of Certain Anticoagulants (Heparin and Hirudin) in Extracorporeal Thrombosis and on the Mechanism of Thrombus Formation, *J. Exper. Med.* **46** 21, 1927.

In brief, the factors which seem to be most concerned in the changes in coagulation time in these experiments are as follows (a) A disintegration of platelets occurs which would give rise to more tissue fibrinogen (Mills), cephalin (Howell) and thrombokinas (Morawitz) This factor would not explain the increase in coagulation time after release of the constriction (b) Changes in the hydrogen ion concentration are in the direction of changes associated with conditions in which the coagulation time is decreased (c) Changes take place in the anticoagulant element (heparin) which would explain both the decrease in coagulation time during constriction of the hepatic veins and the increase in coagulation time after release of the constriction

#### SUMMARY

1 A method of mechanically constricting the hepatic veins in the dog has been described This procedure permits a study of changes occurring in the blood following removal of the liver from, and its return to, the circulation

2 Following this constriction there is a precipitate fall in blood pressure of from 40 to 60 mm of mercury, a level which is then maintained reasonably constant for twenty minutes or more

3 A decrease in the concentration of the blood (an average of 11 per cent in six dogs) with a gradual increase in concentration occur until, at the end of fifteen minutes, the normal value is approximately reached

4 A rapid decrease in blood sugar (average of 42 per cent) is obtained during constriction for fifteen minutes with a rapid rise after release

5 A definite decrease in coagulation time of from 25 to 50 per cent is observed during constriction, followed by an increase on release

6 There was a slight decrease of fibrinogen (11 per cent) during constriction and a definite increase of 25 per cent or more on release of constriction

7 The platelets were slightly decreased (15 per cent) during constriction with slight change on release

8 Changes in blood calcium can be accounted for by dilution

9 The experimental results reported indicate that the chief factors, the interaction of which is concerned in the changes in coagulation time during and after constriction of the hepatic veins, are (a) alterations in antithrombin (heparin) content, (b) increase in the hydrogen ion concentration, and (c) numerical changes in platelets

# OPIUM ADDICTION

## IX WATER BALANCE STUDIES DURING THE ADMINISTRATION AND THE WITHDRAWAL OF MORPHINE <sup>†</sup>

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AND

EDWARD G TORRANCE, M D

PHILADELPHIA

Abiupt withdrawal of morphine from human addicts is practically always associated with loss of weight during the manifestation of the so-called "withdrawal symptoms" During this period, the addicts invariably refuse to take any nourishment, their water intake is practically negligible and increased perspiration is noted It is the object in this paper to report the results of our studies of water balance in five addicts, as well as in three normal persons, given the same diet, in order to determine whether the loss of weight is due entirely to inanition, or in part to an additional loss of water as the result of increased metabolism

### METHODS

Water balance was estimated by the method of difference of weight The diet employed consisted of a modified Folin<sup>1</sup> diet prepared each morning, the ingredients used being eggs, whole milk, cream, malted milk, coffee, vanilla, Welch's grape juice and sugar, as well as 7 Gm of salt and 25 Gm of candy, in addition to water These substances were prepared in various combinations, and administered in the same quantities, at the same hour each day, throughout the experiment The normal subjects, first-year medical students in the School of Medicine of the University of Pennsylvania, who were taking their final examinations in anatomy and chemistry, were able to continue this regimen throughout the seven days of the experiments The addicts succeeded in retaining all food administered while they were receiving their drug Only two, however, accepted and retained the food during the forty-eight hour withdrawal of morphine, and one of these refused the additional water that was included in the day's proffer of food and drink In the table is given the number of calories administered per day together with the amounts of protein, carbohydrate and fat from which the caloric intake was calculated<sup>2</sup>

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<sup>†</sup> From the Narcotic Wards of the Philadelphia General Hospital

<sup>1</sup> The expenses of this research were defrayed by the Committee on Drug Addictions, New York City, and the studies were carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction, in the wards of the Philadelphia General Hospital, which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia

<sup>1</sup> Folin, Otto Approximately Complete Analyses of Thirty Normal Urines, *Am J Physiol* **13** 44, 1905

<sup>2</sup> Lusk, Graham The Elements of the Science of Nutrition, Philadelphia, W B Saunders Company, 1923, p 42



The subjects were weighed exactly at 9 o'clock each morning, on a silk scale of the type proposed by Benedict and Root,<sup>3</sup> the scale weighing accurately to within 10 Gm. The subjects were required to remove all clothing following the weighing, the clothing then being weighed separately and deducted from the total weight obtained. Before being weighed, all subjects were required to pass their urine and defecate if possible. The last administration of a food mixture was given at 3 a. m., the last administration of water, at 6 a. m. Dietetic scales were used to measure to within a gram the amount of food and water taken.

All urine, feces, vomitus and blood were collected and weighed on a scale in the ward, with an accuracy of within 1 Gm. The total collections were again reweighed in the laboratory as a check on the amounts obtained in the ward. Toluene was used to preserve the urine.

The Kjeldahl method was used for the determination of the amount of nitrogen in the urine and dried feces. The amount of uric acid of the urine was determined by the method of Benedict and Franke.<sup>4</sup> The Folin colorimetric method<sup>5</sup> was used to determine the amount of creatinine of the urine. We are indebted to Austin and Sunderman<sup>6</sup> for the method of calculating the water balance.

Throughout this study we have made an arbitrary allowance for maximal error for each measurement and estimate. This allowance for error is designated in text and table by the symbol  $\pm$  and must not be confused with probable error or other statistical function.

#### *Calculation of Water Balance*

Measured intake (grams)

$$(1) I = (\text{food} + \text{beverage} + \text{enema in grams}) \pm 2 \text{ per cent}$$

Measured intake of water (grams)

$$(2) W_1 = (\text{water of food estimated from tables [but not the water of oxidation] + beverage + enema}) \pm 2 \text{ per cent}$$

Water of oxidation of food intake (grams)

$$(3) W_{ox} = (0.413 P_1 + 0.555 C_1 + 1.071 F_1) \pm 2 \text{ per cent in which } P_1, C_1 \text{ and } F_1 \text{ are the grams of protein, carbohydrate and fat in the intake. The amount of water formed by oxidation is taken from Magnus-Levy's calculations that 100 Gm of protein give 41.3 Gm of water, 100 Gm of carbohydrate give 55.5 Gm of water and 100 Gm of fat give 107.1 Gm of water.}$$

Total water intake (grams)

$$(4) W_{t1} = W_1 + W_{ox1}$$

Measured output (grams)

$$(5) O = (\text{urine} + \text{feces} + \text{sputum} + \text{blood removed}) \pm 2 \text{ per cent}$$

Measured water output (grams)

$$(6) W_o = (W_u + W_{fec} + W_{sp} + W_{bl}) \pm 2 \text{ per cent}$$

Daily change in weight (grams)

3 Benedict, F. G., and Root, H. L. Insensible Perspiration. I. Its Relation to Human Physiology and Pathology, *Arch. Int. Med.* **38**: 1 (July) 1926.

4 Benedict, S. R., and Franke, Elizabeth. A Method for the Direct Determination of Uric Acid in Urine, *J. Biol. Chem.* **52**: 387, 1922.

5 Folin, Otto. Beitrag zur Chemie der Kreatinins und Kreatins im Harn, *Ztschr. f. phys. Chem.* **41**: 223, 1904.

6 Austin, J. H., and Sunderman, F. W. Water Metabolism in Pneumonia, to be published.

- (7)  $\Delta W_t = (\text{initial weight—final weight}) \pm 20 \text{ Gm}$  for the period In the estimation of mean increment per day, this allowance for error is divided by the number of days in the period

Weight loss through skin and lungs (grams)

$$(8) -\Delta W_{t_s} = -\Delta W_t - (O-I)$$

Weight loss due to excess of  $\text{CO}_2$  in grams over  $\text{O}_2$  in grams

$$(9) (\text{CO}_2 - \text{O}_2) = 75 \pm 75$$

This range is taken as sufficiently inclusive to cover any reasonable variation in total metabolism and respiratory quotient

Water loss through skin and lungs, neglecting the solids of the sweat, which are assumed to be less than 0.5 per cent of the water loss (grams)

$$(10) W_{s_1} = (-\Delta W_{t_s} - [\text{CO}_2 - \text{O}_2]) \pm \text{error (table may be seen here)}$$

Total water output (grams)

$$(11) W_o = (W_o + W_{s_1}) \pm \text{error (table)}$$

Absolute daily water balance

$$(12) \text{WBal}_{\text{abs}} = (W_{t_1} - W_{t_o}) \pm \text{error (table)}$$

## RESULTS

Examination of the table giving the data relative to the water metabolism shows

1 The three controls and all the addicts, except addict 3, were in water balance within our allowance for error in their first periods, while receiving the drug. Addict 3 in the first period, while receiving the drug, suffered a water loss

2 During the two or three days of withdrawal of morphine, a definite and usually great negative water balance occurred. This occurred in two subjects, addicts 1 and 2, without diminution in the intake of food, although in the latter diminution in fluid intake accounted for half of the loss. Both, however, showed increased water output. In the other three subjects, the diminished intake of food and water was the outstanding feature and it gave rise to a negative water balance in spite of some diminution in the water excretion

3 In the final periods during which the three addicts were studied, after resumption of the drug, the food and water intake was approximately as in the first period. In two, addict 4 and addict 5, there was definite water retention, in neither addict 1 nor addict 4, however, did it in three days compensate for the previous loss

4 When the water loss from skin and lungs is considered as a fraction of the total water loss through skin, lungs and urine, two addicts, nos 1 and 3, exhibited initially a high loss of water through skin and lungs as compared with the controls. One can also recognize in three of the addicts, nos 2, 4 and 5, a relatively greater loss through the skin and lungs during the withdrawal period

# Summary of Water Balance Studies in Normal Subjects and in Human Opium Addicts During Administration, Withdrawal and Readministration of Morphine \*

Subject	Dates	Days in Period	Treat ment	Change in Weight, Gm	Food Intake					Nitro gen Output, Urine Acid and in Feeces, Urine, Gm Mg	Water of Oxida tion of Food, Gm	Total Water Intake, Gm	Water Output of Urine, Gm	Water Output of Skin and Lungs, Gm	Total Water Output, Gm	Water Balance, Gm	$\frac{W_s}{W_u + W_s}$	Creat ining Coeffi cient, Urine
					Protein, Gm	Carboby drates, Gm	Fat, Gm	Calories	Output, Urine and in Feeces, Gm									
Control 1 (K L)	6/ 1 to 6/ 7/28	7	None	- 100 ± 3	102	235	111	2,750	16.6	141	323 ± 6	2975 ± 60	1885 ± 38	1080 ± 98	30.9 ± 138	- 84 ± 198	0.36 ± 0.1	9.51
	6/ 2 to 6/ 7/28	6	None	- 38 ± 3	102	235	141	2,750	16.0	161	323 ± 6	2982 ± 60	1720 ± 34	1231 ± 103	3007 ± 138	- 25 ± 198	0.42 ± 0.6	9.94
	6/ 2 to 6/ 7/28	6	None	- 39 ± 3	102	235	111	2,750	16.2	505	322 ± 6	2982 ± 60	1830 ± 36	1118 ± 101	3003 ± 138	- 21 ± 198	0.38 ± 0.5	8.90
Control 3 (H M)	3/23 to 3/27/28	5	With drug	- 85 ± 4	102	196	138	2,575	13.2	465	299 ± 6	2445 ± 49	1083 ± 22	1111 ± 99	2,621 ± 128	- 76 ± 177	0.51 ± 0.5	8.08
	3/28 to 3/29/28	2	No drug	- 575 ± 10	102	196	138	2,575	16.6	964	299 ± 6	2444 ± 48	1367 ± 27	1468 ± 101	2942 ± 133	- 528 ± 181	0.51 ± 0.5	8.36
	3/30 to 4/ 1/28	3	With drug	+ 5 ± 7	102	196	138	2,575	16.5	535	299 ± 6	2570 ± 51	1340 ± 27	985 ± 101	2,769 ± 133	+ 1 ± 181	0.42 ± 0.6	8.28
Addict 2 (V W)	3/23 to 3/27/28	5	With drug	+ 89 ± 4	101	106	138	2,550	15.8	428	299 ± 6	2442 ± 49	1302 ± 26	878 ± 99	2333 ± 128	+ 109 ± 177	0.10 ± 0.6	7.80
	3/28 to 3/29/28	2	No drug	- 1121 ± 10	101	150	138	2,300	16.9	900	299 ± 6	1977 ± 40	1367 ± 27	1593 ± 96	3077 ± 125	- 1100 ± 165	0.51 ± 0.6	7.07
	2/27 to 3/ 1/28	4	With drug	- 539 ± 5	102	178	135	2,450	16.7		290 ± 6	2747 ± 55	820 ± 16	2013 ± 113	3225 ± 135	- 478 ± 190	0.71 ± 0.7	
Addict 3 (W O)	3/ 2 to 3/ 4/25	3	No drug	- 1494 ± 7	30	52	42	750	19.1		87 ± 2	1406 ± 28	707 ± 14	2093 ± 95	2856 ± 110	- 1150 ± 138	0.75 ± 0.6	
	5/ 6 to 5/ 8/28	3	With drug	- 83 ± 7	104	235	141	2,775	15.1	361	325 ± 6	3163 ± 63	1882 ± 38	1036 ± 100	3250 ± 145	- 87 ± 208	0.36 ± 0.5	9.00
	5/ 9 to 5/10/28	2	No drug	- 1004 ± 10	15	15	19	200	14.2	352	175 ± 4	1697 ± 34	1279 ± 26	1240 ± 91	2318 ± 119	- 1339 ± 163	0.49 ± 0.5	6.71
Addict 4 (W W)	5/11 to 5/13/28	3	With drug	+ 690 ± 7	104	235	141	2,775	17.4	332	325 ± 6	2,663 ± 57	1368 ± 26	787 ± 112	2162 ± 139	+ 701 ± 196	0.38 ± 0.8	8.20
	5/ 6 to 5/ 8/28	3	With drug	- 119 ± 7	104	235	141	2,775	15.9	503	325 ± 6	2860 ± 57	1976 ± 40	918 ± 97	3016 ± 139	- 156 ± 196	0.32 ± 0.4	7.48
	5/ 9 to 5/10/28	2	No drug	- 908 ± 10	19	68	125	1,675	14.3	604	163 ± 3	1672 ± 33	1257 ± 25	925 ± 87	2503 ± 118	- 831 ± 151	0.12 ± 0.5	6.11
Addict 5 (S Z)	5/11 to 5/13/28	3	With drug	+ 809 ± 7	104	235	141	2,775	16.3	377	325 ± 6	2863 ± 57	1187 ± 21	832 ± 114	2078 ± 139	+ 785 ± 196	0.41 ± 0.8	6.61

\* Each calculation represents the mean per day for the period of study

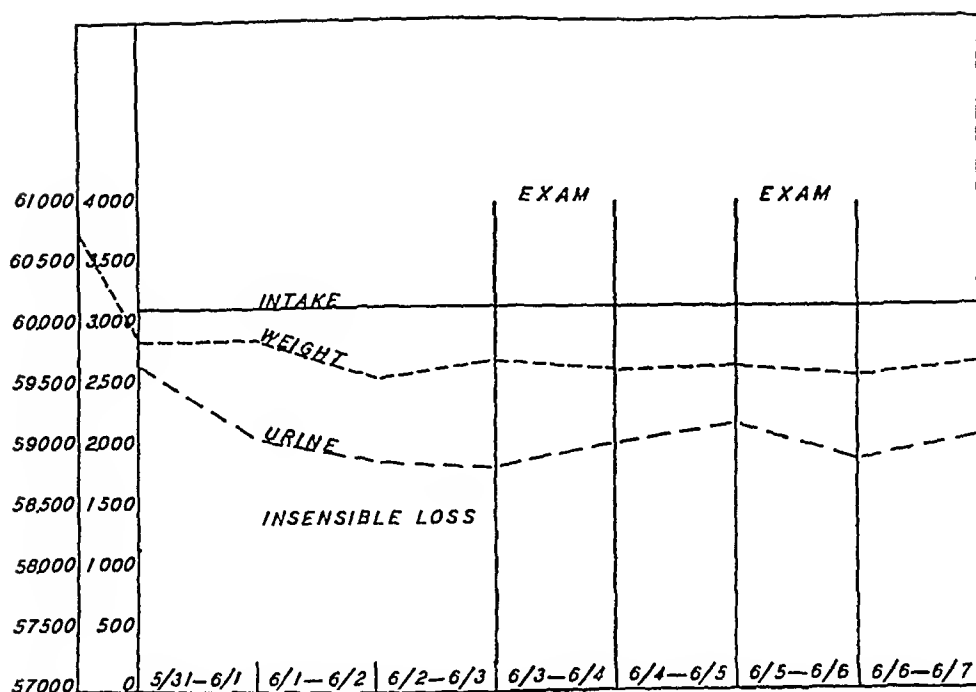


Chart 1—Graphic representation of the daily intake of food, change in weight, urine output and invisible water loss of control 2. The ordinates represent grams

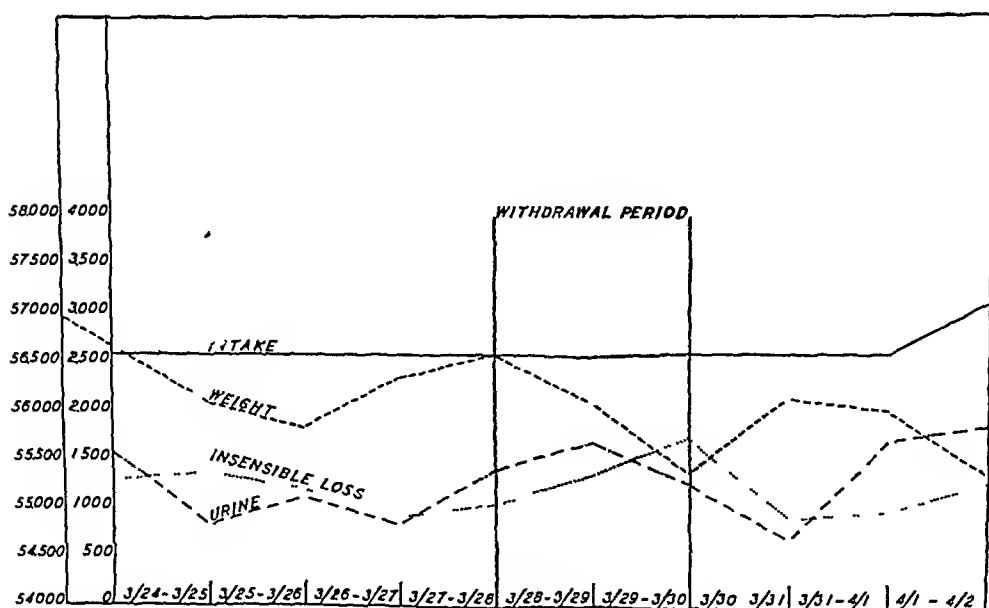


Chart 2—Graphic representation of the daily intake of food, change in weight, urine output and insensible water loss of addict 1. The ordinates represent grams

The explanation of this disturbance in the water balance during the period of withdrawal, had we only the data on addicts 3, 4 and 5, would naturally be the loss of water associated with inanition. This explanation hardly serves for the loss in addicts 1 and 2, unless we postulate an increased metabolism in these subjects during withdrawal. That such may well be the case seems not wholly improbable in view of the restlessness and nervousness of the individual patient during the withdrawal of the drug.

The output of nitrogen, as shown in the short periods studied, showed little or no change even when during the two days of withdrawal of morphine the food intake was curtailed. The output of uric acid shows in both addicts whose food intake during withdrawal was maintained, a definite rise.

All addicts during the first twenty-four hours of withdrawal showed a relative increase in the output of urine followed by a decided fall during the second twenty-four hours of this period. Water loss through skin and lungs, on the other hand, showed a relative increase during the second twenty-four hours compared with that during the initial twenty-four hours of withdrawal.

#### COMMENT

From the data available one can recognize a loss of weight and water during withdrawal. The tendency in three of the subjects to reduce the intake of food and fluid during the withdrawal period was undoubtedly a major factor in bringing this about. In two other subjects, whose food intake remained the same, the loss of weight was possibly an evidence of increased metabolism which may have had no further cause than the nervous restlessness of the individual patient at this time. That there was any more specific effect of the withdrawal of the drug on the water metabolism seems from the data obtained unlikely, but it cannot be absolutely excluded. To attempt a further answer by a study of withdrawal with the addict on a much higher level of caloric intake seems hopeless because of the aversion during withdrawal to even the moderate diet used in this study.

A marked increase in excretion of uric acid detected in addicts 1 and 2 with a constant diet is noted in the table. All other addicts who served as subjects failed to maintain this constant intake. Studies of the uric acid of the blood in four other cases during withdrawal, however, failed to show any significant changes. Schubel<sup>7</sup> found an increased elimination of purine base and phosphoric acid during abrupt withdrawal in dogs, and attributed this to a sudden alteration in the

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<sup>7</sup> Schubel, Konrad. Stoffwechselversuche an Hunden während der Gewöhnung an Morphin und während des Morphinhungers, *Arch f exper Path u Pharmacol* 88 1, 1920

central nervous system which he claimed took place following withdrawal of the drug Sollier<sup>8</sup> attributed the symptoms accompanying withdrawal to marked alterations brought about in glands, particularly the endothelial cells, when morphine is no longer given

The medical students who acted as normal subjects in these experiments were selected with a knowledge of their tendency to worry during examination. It is significant to know that these men retained their normal weight throughout the experiment, and failed to show a negative water balance or any increase in frequency or amount of urine on the two days on which the final examinations were given

#### CONCLUSIONS

Abiupt withdrawal of morphine in a series of human addicts to opium resulted in a negative water balance and, in two of these subjects, an increased elimination of uric acid. The negative water balance was most likely due to failure to take sufficient food and water, although increased loss of water from increased metabolism cannot be entirely excluded, particularly in view of the restlessness of these subjects during withdrawal

The control subjects, three medical students taking their first year final examinations, failed to show a negative water balance, any increase in frequency of urination or in twenty-four hour output, or any loss of weight on the days of the final examinations

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<sup>8</sup> Sollier, P. La demorphinisation. Mechanisme physiologique. Consequences au point de vue therapeutique, *Presse med*, April 23 and July 8, 1898

# HEPATOGENIC HYPOGLYCEMIA ASSOCIATED WITH PRIMARY LIVER CELL CARCINOMA<sup>\*</sup>

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AND

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Deficient liver function has been assumed in certain cases of spontaneous hypoglycemia, but no proved examples of hepatic origin comparable with those apparently due to hyperinsulinism have been reported. The liver appears to be able to maintain an adequate blood sugar level in spite of widespread injury. Although complete removal is followed experimentally by a progressive fall in blood sugar, no marked change in carbohydrate metabolism has been observed after partial removal. The following case of hypoglycemia, apparently of hepatogenic type, is, therefore, of interest.

## REPORT OF CASE

N W, a colored man, a native of Honduras, aged 30, was admitted to the hospital for an exploratory laparotomy on July 6, 1928. He had been in good health prior to January, 1928, when he began to lose weight. In May, weakness was apparent, in June, he was seized with intense epigastric pain after eating. The pain decreased after an hour but a dull ache persisted for a week, there was no nausea or vomiting. Thereafter he had an occasional dull pain after meals and irregular periods of slight fever. On July 9, operation showed a hard, nodular mass the size of a large orange in the left lobe of the liver, a similar mass, the size of a walnut, was present in the right lobe. The pancreas, stomach, duodenum, gallbladder and kidneys appeared normal. Section of a small portion of tumor tissue was reported as adenocarcinoma. Sixteen days after operation, the patient was discharged.

On August 4, twenty-six days following operation, he was readmitted in a comatose state, from which he quickly aroused after administration of orange juice. He had had two previous spells of extreme weakness before breakfast, which were relieved by food. On the morning after admission the blood sugar during fasting was 0.04 per cent, and on the next day 0.053 per cent. Examination showed an emaciated negro, 68 inches (172.7 cm) in height, weighing 113 pounds (51.3 Kg). There was no evidence of jaundice. Slight general adenopathy was present. The thyroid gland appeared to be normal. The heart was normal in size, rate and rhythm, there was a systolic blow over the pulmonic area. The peripheral arteries seemed harder than normal. The blood pressure was 120 systolic and 84 diastolic. The lungs were normal except for a few scattered rales. A rounded, painless bulging, not definitely nodular, was present in

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<sup>\*</sup> Submitted for publication, May 25, 1929

<sup>\*</sup> From Northwestern University Medical School and Wesley Memorial Hospital

the epigastrium, evidently in the left lobe of the liver, the smooth edge of which was palpated just above the navel. The spleen was not palpable, there was no ascitic fluid. The prostate was normal. The reflexes were normal. The blood count and smears showed only slight secondary anemia, the Wassermann and Kahn tests gave negative results. The urine was normal, the phthalein excretion was 45 per cent. The basal metabolic rate was minus 9 per cent. The results of the examination of the eyes were negative except for perivasculitis of the retinal vein. X-ray pictures of the skull showed a normal sella turcica and other bone structures.

Determinations of the blood sugar during fasting were subnormal. The collection of samples during strict fasting was prevented after a few days by the onset of coma, but specimens of blood obtained four hours and later two hours after feedings containing 18 Gm of dextrose gave equally low readings (table).

#### *Blood Sugar Determinations*

	Blood Sugar (Mg per 100 Cc)
8/ 6	40 fasting
8/ 8	53
8/10	32
8/11	52 five hours after 18 Gm of dextrose
8/13	40
8/16	27
8/18	41
8/20	44
8/22	28
8/24	33
8/26	35
8/28	40
8/31	44 four hours after 18 Gm of dextrose
9/ 2	47
9/ 4	25
9/ 6	37
9/ 8	63 two hours after 18 Gm of dextrose
9/10	43
9/18	52
9/21	49
9/24	139 one hour after 18 Gm of dextrose
9/27	81
10/ 1	70
10/ 5	114
11/19	13 terminal

On August 14, tests made before meals and before supplementary feedings at 4 a m and at midnight (total dextrose 384 Gm) showed a subnormal level in every instance except before the noon meal (fig 1). Hypoglycemic attacks recurred during the early morning hours. A diet containing 440 Gm of available dextrose (carbohydrate, 300, protein, 60, fat, 150) with supplementary feedings of 18 Gm of dextrose at 3 and 9 a m, at noon and at 4 and 10 p m, also failed to prevent reactions. After September 13, the extra feedings were given hourly from 11 p m to 7 a m inclusive, and at 9 a m (total dextrose 510 Gm). Finally, on October 9, because of occasional afternoon attacks, feedings at 3, 9 and 10 p m were added (total dextrose 570 Gm). About this time the patient became unable to retain food, after October 16, he could take only irregular light meals and orange juice or dextrose, particularly at the onset of attacks. The afternoon temperatures rose from 99 or 100 to 100 or 101 F. During the intervals between attacks he was normal mentally and showed no toxic effects suggestive of hepatic insufficiency. The reactions became more frequent, occurring from three to seven times a day. They were all of the same character. The first subjective indication was a sense of fatigue followed by dimness of vision which caused the patient to lie down or, when already in bed, to lay aside whatever he was doing. There was no sense of discomfort. He would close his



eyes and forthwith lose consciousness. This phase was characterized by a peculiar staring expression, rolling of the eyes, grimacing and irregular movements of the arms and legs. The sclerae became blood streaked, and the pupils dilated. For some time he seemed to understand what was said to him, but there was no recollection of this afterward. The pharyngeal reflex was usually retained so that orange juice was swallowed when poured into the mouth. The respirations were not labored. The later attacks were associated with delirium. From an ordinarily mild mannered person he became noisy and resentful of his social status and treatment. Attacks of from ten to thirty minutes' duration were observed, they were promptly relieved by the oral administration of dextrose even though, late in the course, he would immediately spit out much of the orange juice. A blood pressure of 160 systolic and 110 diastolic observed during one attack had dropped to 140 systolic and 90 diastolic a few minutes after it was over. The final hypoglycemic reaction occurred on November 19. Dextrose was

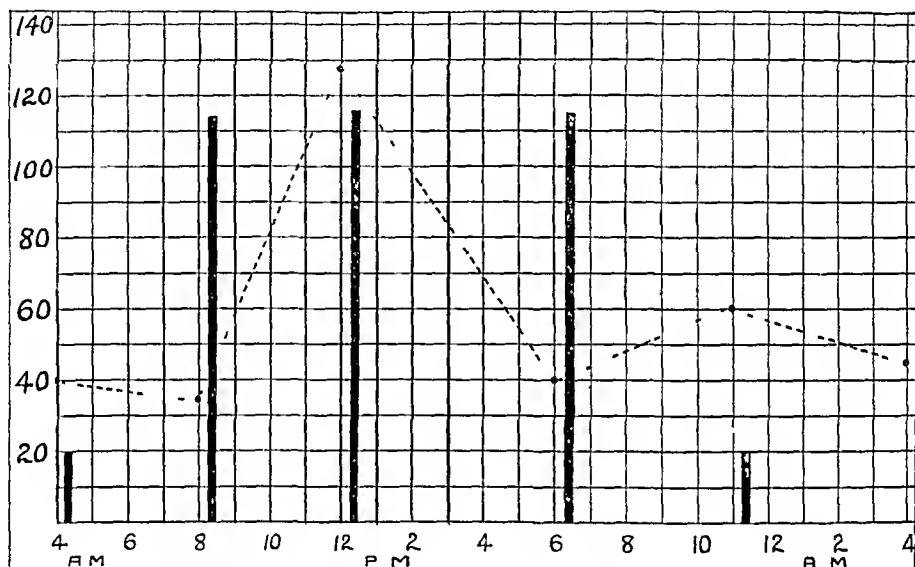


Fig 1—Diurnal blood sugar curve, taken on Aug 13, 1928. The dextrose intake was 384 Gm. The curve represents the milligrams of blood sugar. The heavy black lines indicate the grams of dextrose in the diet.

withheld, through its use life had been prolonged to a point where the patient, unable to eat, passed from one shock to another as soon as the temporary effect of a little orange juice had subsided. Cheyne-Stokes' respirations appeared, a terminal blood sugar reading of 0.013 per cent was obtained, and death occurred from respiratory failure two and a half hours after the onset of the attack.

*Clinical Studies*—On August 14, five hours after a feeding of 18 Gm of dextrose, the blood sugar was 0.045 per cent, the administration of 88 Gm of dextrose produced a maximal rise in the capillary blood to 0.209 per cent in one hour, with readings of 0.206 and 0.158 per cent, accompanied with traces of sugar in the urine after two and three hours, respectively. Tests repeated on September 1 with capillary blood and on September 4 with venous blood showed curves characterized by a rise from subnormal levels to 0.16 per cent in one hour and by a fall to subnormal levels within three hours, indicating a progressive decrease in tolerance (fig 2). Fructose tolerance tests were not made.

On September 27, the injection of epinephrine (1 cc) failed to produce an elevation in the blood sugar level. The initial blood sugar, about two hours after a feeding containing 18 Gm of dextrose, was 0.081 per cent, one-half hour after the administration of epinephrine the reading was 0.057 per cent, in one hour 0.042 per cent and in two hours 0.022 per cent, at which point the patient became comatose. Pituitary extract produced no rise in blood sugar in one hour, at which point the administration of dextrose was necessary. The amylolytic activity of the stool was determined by Wohlgemuth's method as 110.8 and 62.5, on September 19 and October 23, respectively.

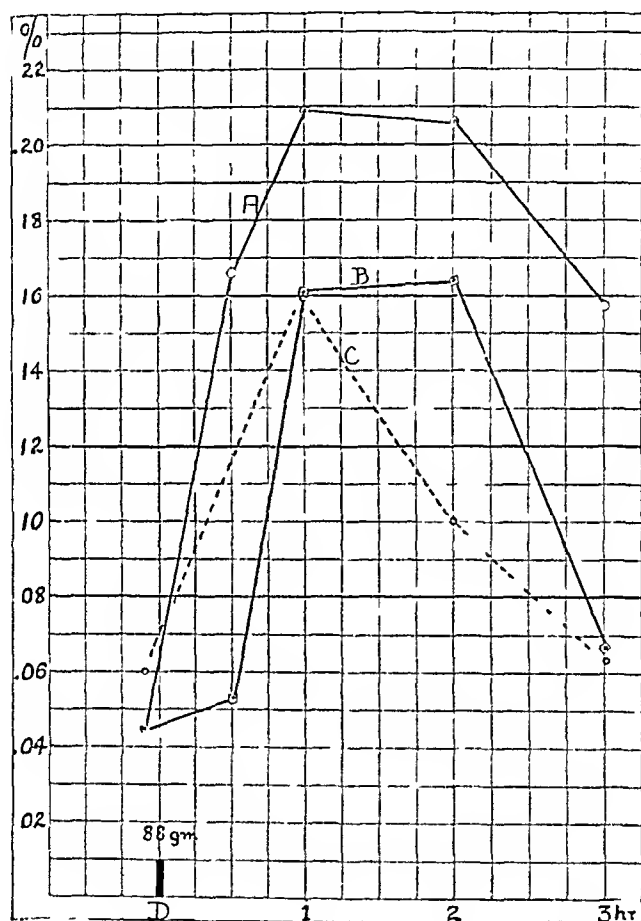


Fig. 2—Curves for dextrose tolerance tests. *A* indicates the curve for the capillary blood taken on August 14, *B*, that for the capillary blood taken on September 1, and *C*, that for the venous blood taken on September 4. *D* indicates the amount of dextrose.

On August 22, the direct van den Bergh test was negative, quantitative determination showed less than 0.7 mg per hundred cubic centimeters of serum. On September 1, the bromsulphalein test for liver function was normal. On the same date, the blood cholesterol was 176 mg. Estimations of the nonprotein nitrogenous constituents of the blood were not made.

The extraction of insulin from 50 cc of the patient's blood as well as from 50 cc of the blood of a normal control was attempted by Mr. I. J. Seitz of the Department of Physiology, none could be demonstrated in either extract by the Fisher modification of the Doisy, Somogyi and Shaffer method.

*Necropsy Report*—The examination was conducted immediately after death by Dr F D Gunn of the Department of Pathology. A summary of the important observations follows. The liver, weighing approximately 3,300 Gm, was distorted in shape, the left lobe, enlarged to about the same mass as the right, contained a nodular, rounded protuberance on its anterior and upper surface at about its middle, the remaining portions were studded with raised, rounded or umbilicated tumor nodules. Projecting from the anterior-inferior surface of the fundus of the gallbladder and covered only by peritoneum were two spherical tumor nodules about 1 cm in diameter, several similar nodules occupied the loose connective tissue around the neck of the gallbladder and cystic duct. Otherwise, there was no involvement of the gallbladder and cystic duct, the extrahepatic



Fig 3—Section through the left lobe of the liver

bile ducts were patent. An irregular tumor mass occupied the wall and a large part of the lumen of the inferior vena cava in the section surrounded by liver tissue. Sections through the liver showed the left lobe and middle portion practically entirely occupied by a more or less lobulated tumor mass, while the right lobe was partly filled with large and small tumor nodules, the remaining part of the liver substance lying at the extreme right portion (figs 3 and 4). Roughly estimated approximately one fifth of the entire liver remained as such. The uninvolved portion was dark red brown, with markings somewhat exaggerated, rather firmer and tougher than normal.

Superficially the pancreas appeared normal, rather soft, and grayish yellow. On macroscopic examination, numerous sections failed to reveal any tumor masses or other pathologic changes. The spleen weighed 840 Gm. Its anterior

surface was rounded, of fairly firm consistency, and was dark purplish red. On section, the surface was smooth, homogeneous and rather dry, it was dark red, and the fibrous stroma was markedly increased, the follicles were not visible, no tumors were found on numerous sections. The brain was normal superficially and after preservation in fixative. The suprarenals were of about normal size, color and consistency, there was medullary substance in fair amount. The kidneys were about equal in size, smooth externally, with capsules stripping cleanly, leaving smooth pale surfaces. On section, the cortex, from 7 to 8 mm in width, was moderately swollen and pale, the markings were distinct. The stomach, duodenum, small intestine and colon showed pale mucosa but no pathologic change, the mesentery was free from enlarged nodes and tumor masses, the



Fig 4—Section through the right lobe of the liver

rectum was hyperemic and moderately edematous. The ureters, urinary bladder and prostate were normal in appearance.

The lungs contained numerous, evenly distributed nodules, ranging in size up to that of a walnut, those on the surface protruded prominently, while the larger ones were umbilicated. On section, the tumor masses were found distributed throughout the lung substance. The lung tissue between the nodules was well aerated except in the posterior portions which showed hypostasis and a moderate quantity of edematous fluid. The mediastinum, especially around the base of the heart, contained fairly numerous tumor-bearing lymph nodes ranging in size up to that of a hazelnut, two of the larger of which encroached on and lay partly in the posterior wall of the right atrium. The heart showed no pathologic change, the coronary arteries were patent and their lumina were of normal

diameters The interior of the aorta showed linear and scattered, irregular, slightly raised yellow areas, especially in the ascending and transverse portions of the arch, the thoracic aorta was relatively free and the abdominal aorta was entirely smooth and normal in appearance A small amount of clear amber fluid was present in the pleural cavity and in the pericardial sac, the abdominal cavity was partly filled with similar fluid

*Microscopic Observation, Section Stained with Hematoxylin and Eosin* (Reported by Dr F D Gunn)—In sections from the liver outside the tumor-bearing areas the larger number of liver cells were pale, swollen and rounded, many of them contained two or more large nuclei and in their cytoplasm there was a large quantity of golden brown granular pigment In the tissue immediately adjacent to the tumor nodules the cells were compressed and atrophic, their nuclei were shrunk and pyknotic There was a considerable quantity of dense fibrous tissue which partly separated the tumor from the parenchyma of the liver In a few areas, the bile ducts showed a simple hyperplasia, elsewhere they appeared normal, even in places where completely surrounded by tumor cells their epithelial lining consisted of a single layer of cells, and the basement membrane was unbroken Nowhere did the bile ducts appear to have taken on neoplastic characters

Sections taken from the large tumor mass in the liver showed irregular cords, plugs of epithelial cells with a variable amount of fibrous tissue separating them from each other Here there was a complete absence of the parenchyma of the liver In many places the fibrous septums were broad, dense and hyalinized The tumor cells were for the most part polyhedral, smaller and darker than the liver cells and arranged as thick cords, several cells deep, along the fairly rich network of capillary sinusoids (fig 5) In other places the cells were large and clear with small, dark nuclei and arranged in small alveoli, separated from each other by thin fibrous septums, resembling, in many respects, hypernephroma

Sections from the tumor masses of the lung closely resembled those in the liver The nodules were sharply circumscribed and surrounded by thin fibrous capsules In the large lymph nodes, the tumor nodules had a somewhat different appearance The blood sinusoids, along the course of which the tumor cells were arranged, were wide The fibrous stroma was abundant The alveoli were much larger than elsewhere, their peripheries were sharply marked off by the blood sinusoids and in many places their centers were necrotic

Sections taken from the head, middle and tail of the pancreas showed nothing remarkable The islets of Langerhans appeared normal in size and number In the spleen the reticulo-endothelial cells of the pulp were markedly increased in size and number, with atrophy of the lymphoid follicles and narrowing of the sinusoids of the pulp Sections from the suprarenals showed nothing remarkable Sections of the kidney showed a striking degree of necrosis and calcification of the cells of Henle's loops, while the remaining portions of the parenchyma appeared normal A special study of the pancreas and tumor tissues was made possible by Prof R R Benslev of the University of Chicago In his opinion, the pancreas was normal and the tumor tissue from the liver was not islet tissue There was neither an obvious increase of islet tissue nor an obvious change in the islets themselves, both A and B cells were present in about normal proportions and both were well charged with the characteristic secretory granules The tumor tissue, tested both by Professor Benslev's neutral gentian stain and by Bowie's combination of ethyl violet and Biebricher scarlet, gave negative results as regards islet granules in both instances There was, therefore, no indication of abnormal production of insulin by the cells of the neoplasm

*Analysis of Autopsy Material*—Prof A C Ivy and Mr I J Seitz of the Department of Physiology gave the following analyses

**Glycogen Content of the Liver** The liver weighed approximately 3,300 Gm, of which roughly 70 per cent was scirrhus One hundred grams of liver tissue free from tumor nodules and an aliquot portion of the tumor were treated quantitatively for glycogen by the Pfluger method The 100 Gm of tumor tissue contained no glycogen, the 100 Gm of liver tissue contained 0.8 Gm of glycogen determined as dextrose

**Extraction of Insulin** The Fisher, Doisy, Somogyi, Shaffer method was used Almost the entire pancreas (from 55 to 60 Gm) was extracted for insulin and the final product dissolved in 40 cc of water Eight hundred grams of tumor

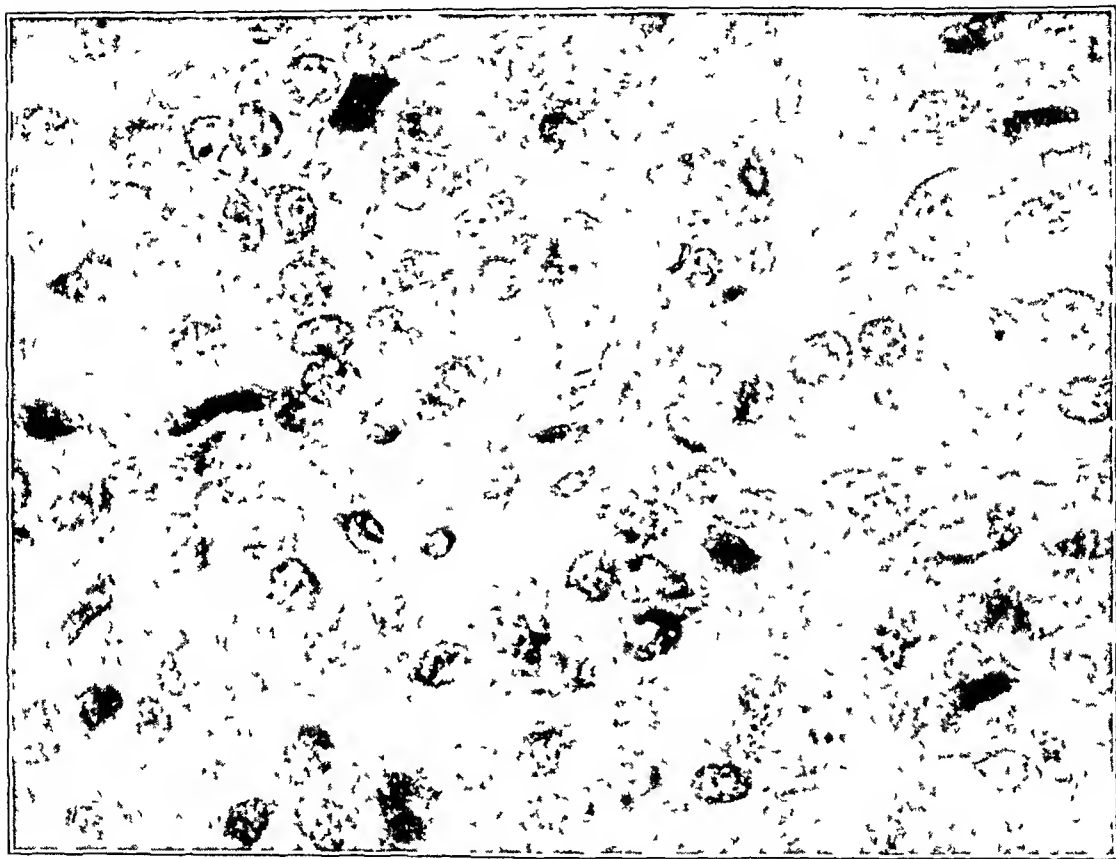


Fig 5—Tumor cells of the liver,  $\times 800$

and a similar quantity of liver tissue were also extracted for insulin, and the final product of each was dissolved in 55 cc of water The usual method of assay was employed The rabbits used weighed from 1,900 to 2,200 Gm and were known by previous experience to react normally to insulin The extract from the liver contained no insulin The extract from the tumor likewise produced no insulin effect, and one rabbit responded to the subcutaneous administration of 5 cc of the tumor extract with moderate hyperglycemia The pancreas contained a minimal normal amount of insulin, about 100 units per kilogram

#### COMMENT

The dominating anatomic feature of this case is a carcinoma which, so far as can be determined, is primary in the liver and of hepatic

cell origin. A large amount (from 70 to 80 per cent) of liver substance was replaced by the neoplasm. The remainder, if comprised of normally functioning cells, would be expected to maintain a glycogen storage balance, in view of the results reported by Mann<sup>1</sup> after experimental removal of part of the liver. The usual signs of hepatic insufficiency were lacking. Clinically, the hypoglycemia syndrome overshadowed all other symptoms. The course resembled in practically every respect the carefully studied case reported by Wilder,<sup>2</sup> which was due to overproduction of insulin, chiefly by liver metastases of a carcinoma primary in the pancreas.

Spontaneous hypoglycemia may be caused by either one of two opposing fundamental conditions, namely hyperinsulinism with excessive consumption of sugar or a deficiency in the glycogen storage or sugar mobilization function of the liver. The former, dependent on production of insulin, of necessity concerns the islands of the pancreas, the latter is concerned with the glycogen storage apparatus, chiefly the liver and muscles. Carcinoma and adenoma confined to the pancreas have caused fatal hypoglycemia,<sup>3</sup> and histologic studies have lent support to the view that spontaneous hyperinsulinism may occur. Wilder's case clearly demonstrates that tumor of the islets with metastases may lead to a fatal hypoglycemia due to hyperinsulinism. No comparable clinical picture of proved hepatic origin has been described. An hepatic origin has been assumed in various instances of spontaneous hypoglycemia, notably in the unusual case reported by Wagner and Parnas<sup>4</sup> in which instability of the blood sugar and negative results with epinephrine were interpreted as evidence of deficient sugar storage or lack of mobilizable glycogen. In various diseases of the liver, such as acute yellow atrophy and cirrhosis, terminal low blood sugar levels have been found. A fatal hypoglycemia appearing in the last weeks of a chronic, apparently infectious disease has been described in rabbits,<sup>5</sup> a progressive decrease in the effect of epinephrine was observed and a characteristic atrophy and fatty degeneration of the liver were found post mortem.

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1 Mann, F. C. Effects of Complete and Partial Removal of Liver, *Medicine* **6** 419, 1927.

2 Wilder, R. M., Allan, F. N., Power, M. H., and Robertson, H. E. Carcinoma of the Islands of the Pancreas. Hyperinsulinism and Hypoglycemia, *J. A. M. A.* **89** 348 (July 30) 1927.

3 Thalheimer, W., and Murphy, F. D. Carcinoma of the Islands of the Pancreas, Hyperinsulinism and Hypoglycemia, *J. A. M. A.* **91** 89 (July 14) 1928. McClenahan, W. U., and Norris, G. W. Adenoma of the Islands of Langerhans with Associated Hypoglycemia, *Am. J. M. Sc.* **77** 93, 1929.

4 Wagner, R., and Parnas, J. K., quoted by Wilder (footnote 2).

5 Oppel, W. W. Zur Frage des hypoglykämischen Symptomenkomplexes bei Kaninchen, *Ztschr. f. d. ges. exper. Med.* **60** 86, 1928.

In the case presented hyperinsulinism can be ruled out since the pancreas was normal grossly and microscopically and since an assay of this organ yielded only a minimal normal amount of insulin. That the tumor cells had not exercised the function of islet cells is indicated by the failure to recover insulin from them and by histologic study.

We must conclude, therefore, that the hypoglycemia was due to a disturbance of the sugar mobilization function of the liver. The tumor contained no glycogen. The quantitative decrease in liver substance to 20 or 30 per cent was certainly an important but evidently not the only factor. After partial removal of the liver in dogs, resulting in a permanent reduction of hepatic tissue, in some cases to less than 15 per cent, Mann found only a slight change in the blood sugar level. Complete removal of the liver, however, is followed by characteristic symptoms associated with a progressive and fatal hypoglycemia, the end can be postponed for many hours by repeated injections of dextrose, but finally symptoms of another type appear which result in death even though the blood sugar level is maintained at, or above, a normal level.<sup>1</sup> Dogs with Eck-fistula develop loss of muscle coordination, staggering gait, weakness, disturbed vision, coma, convulsions and death, symptoms not unlike those of hypoglycemia but due in part to toxemia unrelated to carbohydrate metabolism since they can be relieved not only by dextrose but by Ringer's solution, atropine and gastric lavage.

In the case reported, the functional capacity of the remaining liver cells seems to have been the deciding factor. These cells were mostly pale, swollen and rounded, many containing two or more nuclei and a large quantity of brown pigment, the cells adjacent to the tumor tissue were definitely atrophic. Their glycogen content was unusually low (0.8 per cent). The conclusion seems justifiable, therefore, that in addition to a quantitative loss of liver substance a functional deficiency associated with an inadequate store of glycogen in the remaining cells was present, that the hypoglycemia was hepatogenic due to hypofunction of the residual cells. Under these conditions it is remarkable that symptoms suggestive of hepatic insufficiency, such as toxic manifestations of the type appearing in animals with Eck-fistula, did not appear and that the tests for liver function usually considered of greatest clinical value (the bilirubin content of the serum and the ability of the liver to excrete dye) were negative. The failure of epinephrine to produce a rise in the blood sugar and the abnormally high level produced by dextrose feeding suggested an inability of the liver to store dextrose but could not be considered decisive in view of the similar results in Wilder's case of hyperinsulinism in which the liver was gorged with glycogen.



## SUMMARY

A case of spontaneous hypoglycemia, apparently of hepatic origin, is reported. Attacks of hypoglycemia dominated the clinical picture for three and a half months. Primary liver cell carcinoma, comprising roughly from 70 to 80 per cent of the total liver mass, with metastases in the regional glands, mediastinum and lungs, was found. The remaining liver structure was deficient in glycogen content and showed evidence microscopically of degenerative change. The pancreas contained a normal amount of insulin and presented no signs of pathologic changes. The tumor cells possessed no characteristics of islet cells and contained no insulin.

# TUBERCULOSIS OF THE AORTA

## REPORT OF A CASE<sup>1</sup>

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In 1882, Weigert<sup>1</sup> demonstrated the association between tuberculosis of the vascular system and acute miliaary tuberculosis. The importance of these fundamental studies on tuberculosis of the vascular system is twofold. They demonstrated the damage resulting in the blood vessels themselves and made clear an important route by which tubercle bacilli are disseminated throughout the body.

While tuberculosis of the vascular system is relatively common, tuberculosis of the aorta is still regarded as a rare condition and one that is seldom diagnosed clinically. In reviewing the literature, I have been able to find thirty-six cases, including my own, reported since 1882. The reason the condition is not recognized clinically is that it does not appear to lead to any positive diagnostic signs or symptoms. The pathology, however, as well as the mechanism of the production of the lesion, is well known.

It is generally conceded that tubercle bacilli reach the aorta by one of two routes: first from the blood stream by direct implantation on the intima, or by the vasa vasorum, and second, from without, by the direct extension of a tuberculous process to the adventitia. Of the former type there have been sixteen cases reported, and of the latter, twenty cases, including mine.

The primary involvement of the vasa vasorum has not been demonstrated in man. The French writers Petit and Germain,<sup>2</sup> however, reported three cases of tuberculosis of the aorta in dogs, in which, they claimed, the primary lesions were in the vasa vasorum.

The condition resulting from direct implantation of tubercle bacilli on the intima of the aorta has been called tuberculous endoaortitis. The lesions consist of large or small flattened nodules or, even more commonly, polypoid-like growths. Their development and course are similar to those of tuberculous processes elsewhere. Wooley,<sup>3</sup> in 1911, divided these primary intimal cases into acute and chronic endoaortitis, and stressed as others have, the possible importance of the chronic type.

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<sup>1</sup> From the Pathological Laboratory, The Montreal General Hospital.

1 Weigert, P. *Virchows Arch f path Anat* **88** 307, 1882.

2 Petit and Germain. *Bull soc d'etudes sc de la tuberc*, 1911-1912, *Arch de med exper et d'anat path* **25** 469, 1913.

3 Wooley, P. G. *Bull Johns Hopkins Hosp* **22** 82, 1911.

in the production of general military tuberculosis. He also suggested that the acute aortic lesions are *à part* rather than a source of general military tuberculosis, while the chronic cases may eventually lead to this condition.

Cases of chronic intimal tuberculosis have been reported by Benda,<sup>4</sup> Aschoff,<sup>5</sup> Longcope,<sup>6</sup> Schmorl,<sup>7</sup> Gaylord,<sup>8</sup> Simnitsky,<sup>9</sup> Lucksch,<sup>10</sup> and Paiseau and Lambling.<sup>11</sup>

Cases of acute intimal tuberculosis include those reported by Marchand,<sup>12</sup> Huber,<sup>12</sup> Schuchardt,<sup>13</sup> Hanot,<sup>14</sup> Hanot and Levi,<sup>15</sup> Simnitsky,<sup>9</sup> Blumer,<sup>16</sup> Flexner,<sup>17</sup> and Wooley.<sup>3</sup>

The cases in which the aortic involvement was due to extension from without are those reported by Dietrich,<sup>18</sup> Kamen,<sup>19</sup> Hanau and Sigg,<sup>20</sup> Schmorl,<sup>7</sup> Buttermilch,<sup>21</sup> Councilman and Mallory,<sup>22</sup> Leifmann,<sup>23</sup> Hedinger,<sup>24</sup> Ribbert,<sup>25</sup> Bauer,<sup>26</sup> Le Noble,<sup>27</sup> Dafoe,<sup>28</sup> Zrunek,<sup>29</sup> Kornitzer,<sup>30</sup> Vanzetti,<sup>31</sup> Moriani,<sup>32</sup> and Garolamo Dal Lago.<sup>33</sup>

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4 Benda *Ergebn d allg Path u path Anat*, 1901, vol 6

5 Aschoff *Verhandl d deutsch path Gesellsch*, 1899, 1890, pp 419-421

6 Longcope *Bull Johns Hopkins Hosp* **12** 27, 1901

7 Schmorl *Munchen med Wchnschr* **49** 1379, 1902

8 Gaylord, in *Allbutt System of Medicine*, 1909, cited by Forssner and Longcope

9 Simnitsky *Allm sven Lakartidn* **1** 817, 1901, cited by Forssner

10 Lucksch *Centralbl f allg Path u path Anat* **15** 190, 1904

11 Paiseau and Lambling *Presse med* **34** 1122, 1926

12 Quoted by Weigert (footnote 1, p 360). The case of Gaylord (footnote 8) cited by Forssner and Longcope could not be found in the references given.

13 Schuchardt *Virchows Arch f path Anat* **88** 46, 1882

14 Hanot *Semaine med* **15** 281, 1895

15 Hanot and Levi *Arch de med exper et d'anat path* **8** 784, 1896

16 Blumer *Am J M Sc* **117** 19, 1899

17 Flexner *Bull Johns Hopkins Hosp*, August, 1891, p 120

18 Dietrich *Ztschr f Heilk* **9** 97, 1898

19 Kamen *Beitr z path Anat u z allg Path* **17** 416, 1895

20 Hanau and Sigg *Mitt a Klin u Med Inst der Schweiz* **4** 173, 1896

21 Buttermilch *Inaug Diss*, Berlin, 1898

22 Councilman and Mallory *Med & Surg Rep*, Boston City Hosp, 1896, cited by Haythorn

23 Leifmann *Centralbl f allg Path u path Anat* **15** 749, 1904

24 Hedinger *Frankfurt Ztschr f Path* **2** 121, 1909

25 Ribbert *Sitzungsb d Niederrhein Gesellsch f naturh Heilk zu Bonn* 1910

26 Bauer *Wien klin Wchnschr*, 1912, p 1289

27 Le Noble, E *Arch d mal du coeur* **15** 677, 1922

28 Dafoe *Edinburgh M J* **32** 291, 1925

29 Zrunek *Centralbl f allg Path u path Anat* **25** 577, 1914

30 Kornitzer *Med Klin* **16** 361, 1920

31 Vanzetti *Arch sc medic*, 1908

32 Moriani *Virchows Arch f path Anat* **202** 283, 1910

33 Garolamo Dal Lago *Morgagni Giornale Indirizzato al Progresso della Medicina*, 1913

In the cases of Dietrich and Kamen the aorta was involved from adherent tuberculous bronchial lymph nodes, and in Kamen's case this was followed by rupture of the aorta and acute miliary tuberculosis.

In Buttermilch's case, the aortic involvement was secondary to vertebral disease. Schmorl reported two cases of perforation of the aorta as a result of a tuberculous process: one secondary to a tuberculous lymph node and another secondary to a tuberculous pulmonary cavity. In both, acute miliary tuberculosis resulted.

In Hanau and Sigg's case, a tuberculous aneurysm ruptured into a tuberculous cavity in the lung.

Councilman and Mallory demonstrated a false aneurysm of the thoracic aorta secondary to extension from a tuberculous lymph node, from which acute miliary tuberculosis resulted.

Leifmann demonstrated a case of rupture of the aorta secondary to a caseous mediastinal lymph node, in which acute miliary tuberculosis developed.

Hedinger's patient had tuberculosis of the adventitia associated with subacute miliary tuberculosis, tuberculous basilar meningitis and a solitary tuberculous nodule in the cerebellum.

Ribbett's paper dealt with a case in which there was a communication between the lumen of the aorta and a tuberculous cavity in the lung, which was secondary to tuberculosis of the vertebrae. General miliary tuberculosis followed.

Ziuneck described a case of tuberculosis involving the abdominal aorta in the region of the celiac axis, which led to rupture and death.

In 1920, Koinitzer reviewed eleven cases of ruptured tuberculous aneurysms that had been reported up to that date, and added a case of Professor Stoerk's of Vienna. Stoerk's case was one of rupture of the ascending aorta 1 cm. beyond the aortic cusps and was due to a tuberculous process which began in a group of adjacent lymph nodes. The edges of the rupture were thinned, and the walls of the aneurysms showed an extensive tuberculous process involving two thirds of the media.

Vanzetti's paper, published in 1908, was based on a case of ruptured tuberculous aneurysm of the arch of the aorta, which originated from a tuberculous process in the vertebra and infiltrated the posterior mediastinum. The aortic wall was involved over a considerable area, and at one point the process reached as far as the outer border of the intima and at other points, to the internal layers of the media. Opposite the tuberculous area of the aortic wall was a large prevertebral caseous mass.

Mariam described a case of tuberculosis of the ascending arch of the aorta following tuberculous pericarditis. The process extended for some distance beyond the pericardium. There was an associated hyperplasia of the intima. The media was weakened functionally and "bulging" had occurred.

In 1913 Gerolamo Dal Lago reviewed the literature and added the report of a case of tuberculous mediastinitis in a young patient, which infiltrated the esophageal and aortic walls, leading to the formation of an esophageal ulcer and subsequently to an esophageal-aortic fistula. Death resulted from hemorrhage.

Bauer found an extension of tuberculosis of a lymph node to the arch of the aorta.

LeNoble described a tuberculous aneurysm of the first portion of the aorta.

Dafoe reported two cases of ruptured aneurysm of the abdominal aorta due to tuberculosis.

My case is the twentieth recorded case of tuberculosis of the aorta due to direct extension from without.

#### REPORT OF CASE

*History*—A man, aged 56, a laborer, born in Canada, was admitted to the Montreal General Hospital in the service of Dr. Campbell P. Howard on Nov. 15, 1927, complaining of "swelling of the legs, cough, pain in the right side, itchiness of the skin, yellow vision, shortness of breath, occasional coldness, whiteness and loss of sensation in the distal phalanges of both hands."

One sister had died of pulmonary tuberculosis. His wife, who had died of probable angina pectoris at the age of 55, had had eleven pregnancies, one of which terminated in miscarriage, nine children died in infancy, and one was alive and well.

The patient had not worked for the past two years. He had smallpox as a child. There was no history of syphilis. A cough, unaccompanied by pains in the chest or expectoration, had been present ever since he could remember. He had complained of occasional swelling of the feet and ankles which would disappear over night.

The present illness began about April, 1927, with loss of appetite and a marked swelling of the feet and legs. Soon after, shortness of breath appeared and became a distressing symptom, pain in the left side of the chest developed, this grew worse when he coughed. About this time, a small amount of blood was coughed up. Later, pain was felt over the right side of the chest, this had persisted.

Because all the symptoms were progressing in spite of rest at home, he was admitted to the hospital in November, 1927, seven months after the onset of the present illness.

*Physical Examination* (Dr. C. P. Howard)—The patient was sallow, dyspneic and orthopneic, he coughed frequently but did not expectorate. The mucous membranes were pale and cyanotic. The lymphatic system was normal. The thorax was of the long type, with bony landmarks and deep infraclavicular and supraclavicular fossae. The back was bowed. The upper part of the left side of the chest, anteriorly, was definitely flatter than the right, and expansion here was practically nil. Tactile fremitus was diminished in the left axilla. The percussion note was impaired on the left from the second rib to the base of the axilla and over the base posteriorly. Resonance was present on the right, but the note was impaired over the base. Over the areas of dullness, the breath sounds and vocal resonance were suppressed. Elsewhere, there were many fine moist rales. The pulse rate was rapid, 90 per minute, regular and of small volume. The vessel wall was just palpable. The blood pressure was 145 systolic and 102 diastolic. There was a slight precordial fulness of the heart, but no visible pulsation. The point of maximum impulse could be best felt in the fifth interspace, 12 cm. from the midline. The relative cardiac dullness extended to the level of the second interspace above,

6 cm to the right and 15 cm to the left of the midline. The heart sounds were distant. No murmurs or accentuations were made out, but there was a tendency to gallop rhythm. The remainder of the physical examination showed nothing of importance, except some edema of the legs and feet.

The blood count showed red blood cells, 4,310,000, white blood cells, 7,200, hemoglobin, 50 per cent. The differential count gave polymorphonuclears, 74 per cent, lymphocytes, 25 per cent and eosinophils, 1 per cent.

On Nov 17, 1927, Dr. Richie made the following report of the roentgen examination of the chest: "The heart appears to be increased in the transverse diameter, the arch of the aorta widened. There is evidence of a collection of fluid at both bases, more marked on the left side than on the right. The other shadows seen throughout the lung fields are, I believe, secondary to the cardiac condition rather than due to any definite infection."

The electrocardiogram showed inversion of the T wave. The urea concentration factor was only 18. The Wassermann reaction of the blood was 3 plus on two occasions. The fundi showed one or two scattered hemorrhages.

During the patient's stay in the hospital, a period of five months, the clinical signs and symptoms, as well as the general appearance, varied from time to time, yet there was gradual failure and certain features were always prominent: precordial pain, nocturnal paroxysms of dyspnea, evidence of decompensation of the heart, necessitating bleeding and repeated courses of digitalis, the presence of chronic nephritis at laboratory examination, which gradually became more and more pronounced, an enlarged and tender liver, a sallow color, dilatation of the arch of the aorta and a 3 plus Wassermann reaction on two occasions. A pericardial friction rub, though suspected and often looked for, was present on only one occasion.

The clinical and laboratory observations, apart from those concerning the progressive chronic nephritis, are of special interest with reference to the postmortem examination. The nocturnal paroxysms of dyspnea, the precordial pain, widening of the arch of the aorta, the positive Wassermann reaction and the sallow complexion strongly suggested syphilis of the aorta as one of the pathologic conditions.

The final clinical impression of the case was (1) chronic interstitial nephritis, (2) aortitis syphilitica, (3) cardiac decompensation and (4) auricular fibrillation.

*Autopsy*—The anatomic diagnosis was as follows: (1) hypertrophy of the heart, (2) chronic diffuse nephritis, (3) tuberculosis of the lungs, pleura (left), peribronchial and mediastinal lymph glands, pericardium and aorta, (4) tuberculous pleural effusion (right), (5) chronic passive congestion of the lungs, liver and spleen, (6) acute congestion of the cerebral vessels, and (7) arteriosclerosis of the aorta (slight).

Pathologic examination revealed the following. Macroscopically, the heart was increased in size and weight. The greatest transverse diameter was 15 cm in situ, while the weight, with the pericardium attached, was 830 Gm. There were old fibrous adhesions between the pericardium and both pleurae, more marked on the left side. The pericardial cavity was completely obliterated by fibrous adhesions, in which blood vessels were quite numerous. While the obliteration of the sac was complete, the density of the adhesions which led to it varied. They were most dense over the apical regions and at the base. When the two layers of the pericardium were forcibly separated, a great many small, grayish, discrete and confluent tubercles were visible. They were not uniformly distributed, but occurred in large and small irregularly outlined areas. Collectively, they were most numerous throughout the apical region. No gross caseation was seen. The

mediastinal lymph glands were deeply pigmented with carbon, and some of them showed a tuberculous process. The left side of the heart was markedly hypertrophied, and the right side was dilated. The valve measurements were tricuspid, 14 cm, pulmonary, 9 cm, mitral, 10 cm, aortic, 7 cm, eustachian, 2.5 cm, and coronary, 1 cm. The tricuspid valve was slightly increased in circumference, while the aortic ring was neither enlarged nor thickened. The musculature was of a uniform, pale brown and was firm in consistency. The valves and endocardium were normal. The coronary arteries were patent throughout. Beyond the pericardial cavity, there was no gross evidence of tuberculous involvement of the great vessels of the heart or the tissues immediately about them.

The first portion of the aorta showed the intima to be smooth and glistening with only a few small, noncalcareous plaques about the orifices of the coronary

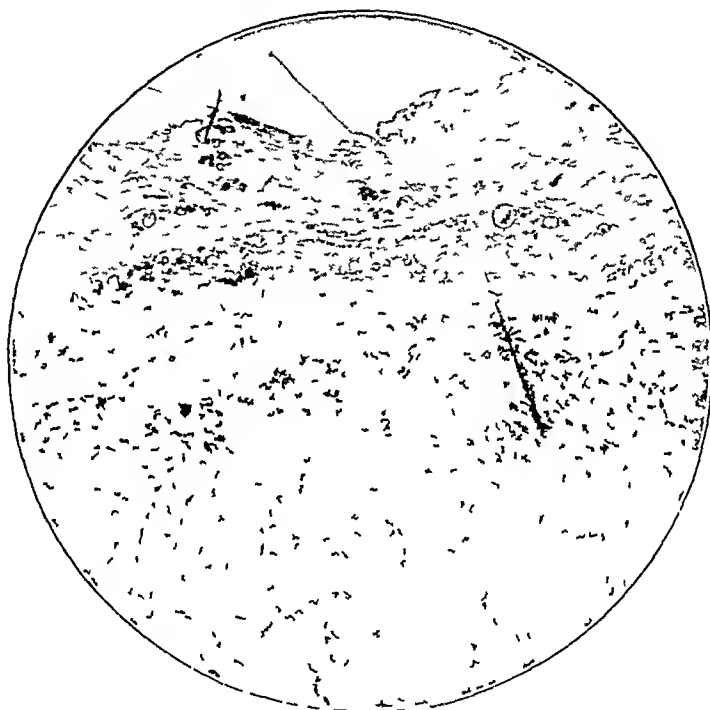


Fig 1—Tuberculosis of the pericardium. Section through the parietal and visceral layers, including the heart muscle. The obliteration of the pericardial sac should be noted.

vessels. In the lower abdominal portion of the aorta, there were also a few raised, yellowish plaques. At no place was there wrinkling or stellate scars visible in the intima, suggesting syphilis.

Microscopic examination of the heart (figs 1 and 2) revealed the following. The two layers of the pericardium were united by a mass of inflammatory granulation tissue which was undergoing organization and had led to obliteration of the pericardial sac. The visceral layer was greatly thickened and edematous and showed on its inner surface tuberculous granulation tissue with numerous characteristic tubercles. Tubercle bacilli were demonstrated within the caseous areas. The muscular fibers were uniformly increased in size and showed indistinct markings of the cross striations. There was no evidence of fibrosis.

Numerous sections were taken from various levels of the aorta. Those taken from the first portion, within 3 cm of the aortic ring and immediately beyond the level of the pericardial reflection, showed the intima regular in outline and well preserved. There was no scarring or round cell infiltration about the vasa vasorum in the adventitia to suggest syphilis. The adventitia, as well as the periadventitia, showed inflammatory granulation tissue, with characteristic tubercle formation and numerous giant cells (figs 3 and 4). At one point (fig 5), this tuberculous process involved the outer portion of the media. Tubercle bacilli were demonstrated in this tissue. Verhoff elastic tissue stain showed no lesion of the vasa vasorum. Sections taken from various other levels, including the abdominal portion, showed no evidence of syphilis or tuberculosis. There was only a moderate arteriosclerosis.

The right lung weighed 700 Gm. It was mottled and grayish-black, its

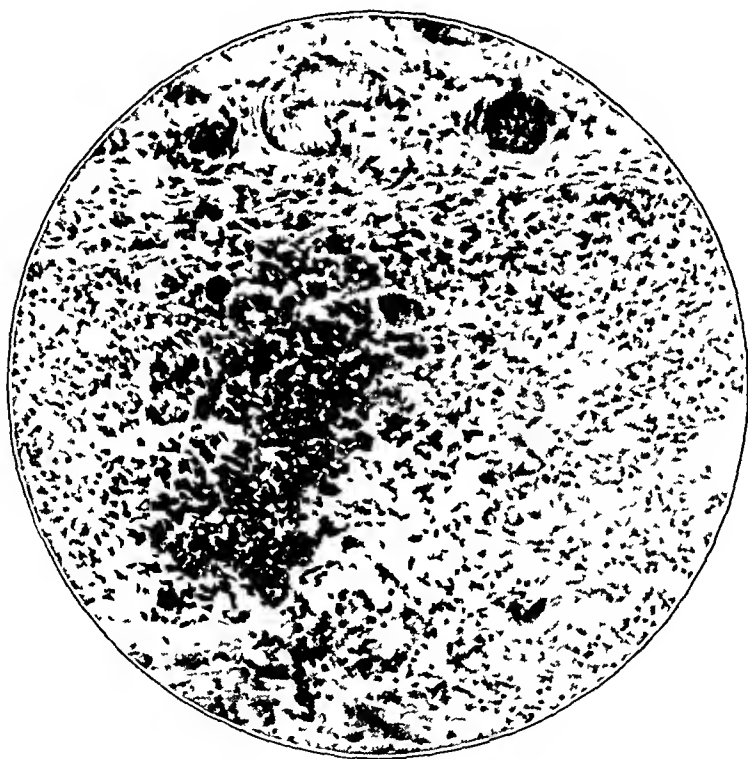


Fig 2—Tuberculous lesion of the pericardium. The giant cells and the tuberculous granulation tissue should be noted. High power magnification.

pleura was smooth, moist and glistening, except for a puckered scar 3 cm in diameter at the apex, and a few recent tubercles at the base. The lung was collapsed and subcrepitant throughout. Serial sections from 1 to 2 cm thick, made throughout the lung from apex to base, after fixation, showed slight compensatory emphysema of the upper lobe. The lymph nodes at the hilum were slightly increased in size, deeply pigmented with carbon and showed caseous tuberculosis.

The left lung weighed 800 Gm. There was obliteration of the left pleural cavity which had, in part, resulted from fibrous adhesions of the two surfaces and in part from a fairly acute exudative process. The fibrous adhesions were most marked throughout the apical region, the anterolateral aspect and along the under surface of the lung where it was firmly bound to the diaphragm. The acute exudative tuberculous process was most marked throughout the posterior aspect and was reflected on to the superior surface of the diaphragm posteriorly. The



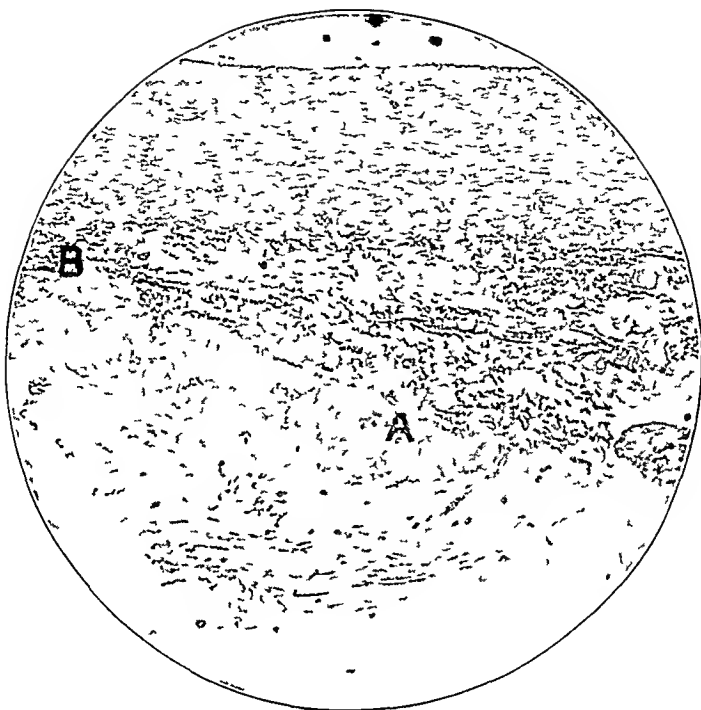


Fig 3—A transverse section through the aorta and the periaortic tissues *A* indicates the large tuberculous area in the periaortic tissues and *B*, the tuberculous involvement of the adventitia

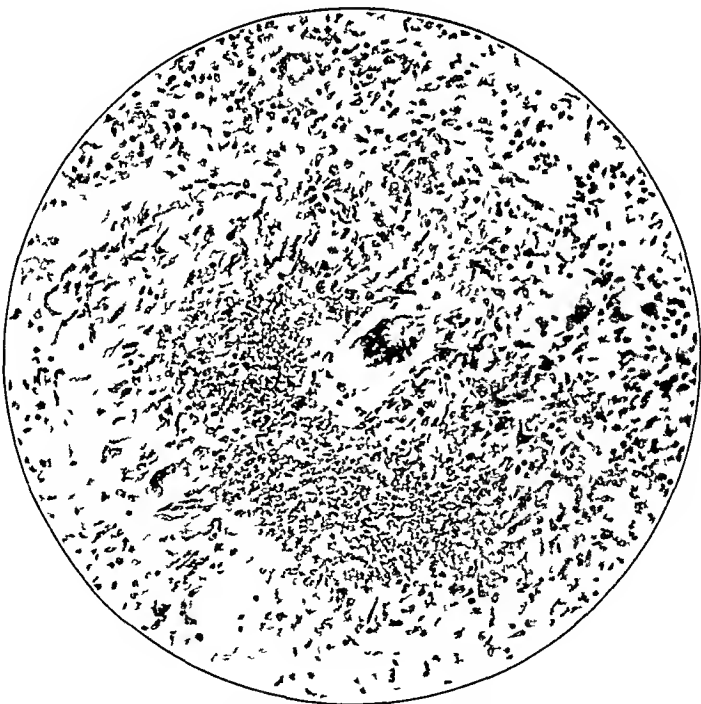


Fig 4—High power magnification of figure 3 at *A* The giant cells and tuberculous tissues should be noted

acute process showed a thick, rather dry, friable, semicaseous material which covered, as a continuous sheet, the visceral layer of the pleura and the parietal layer opposite it. This thick exudate could be readily scraped off. The pleura of this lung was thickened throughout, because of a definite increase in fibrous connective tissue. It was not only increased in consistency, but in some areas it was almost cartilaginous. Serial transverse sections from 1 to 2 cm thick, from apex to base, after fixation showed a marked anthracosis irregularly distributed throughout the lung. In the upper lobe, about its center and 4 cm from its apex, there was a sharply outlined, pale, grayish-white, firm tuberculous nodule, 3 mm in diameter, with a well demarcated peripheral zone composed of deeply pigmented, dense, homogeneous connective tissue. There was a similar area in the lower lobe near one of the secondary bronchi. None of the foci showed calcification. After careful search with a hand lens, no other gross tuberculous foci were demonstrated.

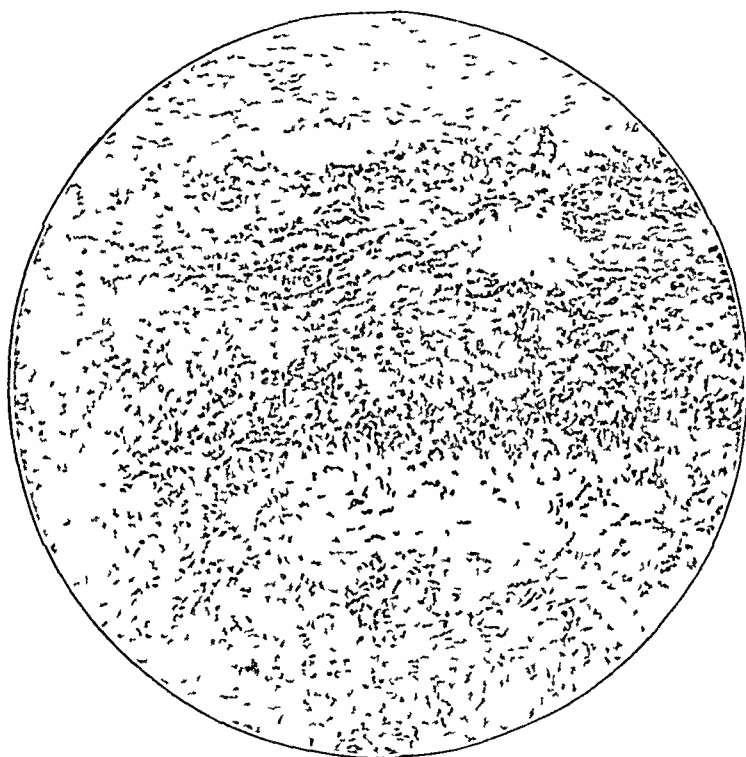


Fig 5—Tuberculosis of the adventitia. The margin of the media is shown at *A*.

in the lungs. The peribronchial lymph nodes were deeply pigmented with carbon and showed caseous tuberculosis.

Microscopic examination of sections from the lungs showed marked congestion and partial atelectasis of the right lung. The left lung showed tuberculosis of the pleura, marked edema and congestion and one microscopic tubercle in the lung parenchyma. Sections from the peribronchial glands showed areas of caseous tuberculosis in which tubercle bacilli were demonstrated.

#### COMMENT

This case falls readily into the second group of lesions of tuberculosis of the aorta, namely, that due to direct extension from outside the vessel wall. However, it presents several interesting features,

some of which were not referred to in the cases previously reported. Acute milary tuberculosis was not present. The lesion in the aorta was not of sufficient extent to lead to perforation and its accompanying milary tuberculosis. Pulmonary tuberculosis was found, not as an active ulcerative form, but as old healed apical scars with two small caseous nodules, while the microscopic examination revealed a third isolated tubercle. On the other hand, there was an extensive acute tuberculous involvement of the left pleura and dense fibrous adhesions obliterating the pleural cavity and extending to the pericardium. The peribronchial and mediastinal lymph nodes and the pericardium also showed an active tuberculous process. It seems quite reasonable to suppose that the tuberculous process started originally in the lung, and then involved the pleura, the bronchial and mediastinal group of lymph nodes, as well as the pericardium and periaortic tissue, and finally the aorta itself. In the other somewhat similar cases reported, with the exception of Mariani's, a tuberculous mass or a tuberculous lymph node was always found attached to or in the vicinity of the aorta. In this case, however, no gross tuberculous tissue could be found attached to the aorta, outside the pericardial cavity, and it was only after a microscopic examination of the aorta that the true condition was revealed. This tuberculous process was found limited to the first portion of the aorta. The most interesting features clinically were the signs and symptoms that led to the diagnosis of aortitis syphilitica, namely, the history, the paroxysms of dyspnea, the precordial pain, the positive Wassermann reaction and the x-ray report of widening of the arch of the aorta. The similarity of the signs and symptoms to syphilis of the aorta might be explained by the site and character of the lesion and the fact that clinical signs and symptoms may depend more on gross lesions than on the action of any specific toxin.

#### SUMMARY

- 1 Thirty-six cases of tuberculosis of the aorta have been reported.
- 2 The case cited here is the twentieth reported instance of tuberculosis reaching the aorta by extension from a tuberculous process outside the aorta.
- 3 In this case the involvement extended to the media but no rupture occurred.
- 4 Clinically, syphilitic aortitis was suspected on account of the history, shortness of breath, pain, pallor and the positive Wassermann reaction.

# BOECK'S SARCOID

REPORT OF A CASE WITH VISCERAL INVOLVEMENT<sup>1</sup>

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Reports of Boeck's sarcoid with visceral involvement are uncommon. When on postmortem examination of our patient it was noted that lesions similar to those of the skin co-existed in the epicardium, in the bronchial mucosa and in the mucosa of the ileum, the problem of the etiology of the malady and its significance to internal medicine was brought anew to our attention.

## BOECK'S SARCOID

In 1899, Boeck<sup>1</sup> for the first time described a cutaneous malady which since has been known as Boeck's sarcoid. In 1900,<sup>2</sup> he described three additional cases of it. The disease is chronic and it is characterized by the presence on the skin of either small or large nodules or infiltrated plaques, varying in number from one to many hundreds. These lesions occur usually at some point on the face, whence they may spread to other parts of the face and may gradually involve the extremities and the trunk. Each single papule or nodule requires months, sometimes years, for its development and for the various stages of its course. The efflorescence may appear under various aspects. Often the eruption appears suddenly, the skin being red and swollen and the seat of an itching sensation. In other cases, a distinct papule appears on the affected skin surface, sometimes the papule is only felt under the skin. The nodule or plaque is usually bright red, bluish red or brownish red. Later in the course it is bluish red in the center and yellowish brown at the periphery. The nodule or plaque may involute without therapeutic intervention, leaving a pigmented atrophic scar. This may last for a

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<sup>1</sup> Submitted for publication, June 1, 1929.

<sup>2</sup> From the Departments of Medicine, Pathology and Dermatology, Jefferson Medical College.

1 Boeck, C. Multiple Benign Sarcoid of the Skin, *J. Cutan. Dis.* **17** 543, 1899.

2 Boeck, C. Abstr. *J. Cutan. Dis.* **20** 38, 1902.

long time and is a characteristic phase of the malady. The nodule or plaque may also show a network of capillaries in the central area. The nodule feels hard, and often, on pressure with a glass slide, shows a minute yellow focus, this led to the name of milium lupoid. The latter term is more desirable, as the term sarcoid is unwarranted, the resemblance to sarcoma, if any, being remote.

Darier<sup>3</sup> from the study of the records of cases in the literature, divided sarcoids into four groups as follows: (1) the multiple benign sarcoid of Boeck, (2) the subcutaneous sarcoid of Darier and Roussy, (3) the nodular erythematous induration-like sarcoid of the extremities, and (4) the Spiegler-Fendt sarcoid. This classification was at one time adhered to by dermatologists and still may be found in all textbooks on cutaneous diseases. However, at present, of the four groups, Boeck's sarcoid and Darier and Roussy's sarcoid are the only two types that are accepted by dermatologists as clinical entities. Treatment is ineffective, except that under prolonged use of arsenic the lesions involute. There is a strong suggestion of coincidence. One of the characteristics of this efflorescence is that the lesions disappear leaving atrophic pigmented spots, without therapeutic intercession.

#### ETIOLOGY

With the report of our case, it was our intention to review the literature related to the subject. This has been done completely by Goeckerman<sup>4</sup>. His careful resume of the observations on sarcoid and related lesions throws the entire subject into relief and serves as a background for the proper appraisal of what is known and also what is still in controversy with regard to the etiology of the sarcoid.

Reschin,<sup>5</sup> as well as Kuznitzky and Bittorf,<sup>6</sup> considered the condition as a definite disease entity. On the other hand, many investigators view the sarcoid as a symptomatic manifestation of various diseases. However, the ruling thought appears to be that Boeck's sarcoid is caused by the tubercle bacillus and that the cutaneous lesion is a manifestation of sensitization in a patient whose epithelial cells have previously been sensitized to a tuberculous antigen. The clinical appearances that the lesion may assume and its morphologic variation from other tuberculous lesions

3 Darier, J. Die cutanen und subcutanen Sarcoid. Ihre Beziehungen zum Sarcom zur Lymphodermie, zur Tuberkulose, *Monatshr f prakt Dermat* **1** 419, 1910.

4 Goeckerman, W. H. Sarcoids and Related Lesions, *Arch Dermat & Syph* **18** 237 (Aug) 1928.

5 Reschin, M. Universelles benignes Miliumlupoid Boeck's mit Beteiligung innerer Organe, *Arch f Dermat u Syph* **139** 30, 1922.

6 Kuznitzky, E., and Bittorf, A. Boecksches Sarkoid mit Beteiligung innerer Organe, *Munchen med Wchnschr* **62** 1349, 1915.

of the skin depend on the manner in which the particular patient reacts to the tuberculous antigen. An attentive reading of the literature with reference to the etiology of the disease seems to favor tuberculosis as the origin of Boeck's sarcoid. Nevertheless, a notable point is scored by those who are opposed to the hypothesis that the condition is tuberculous. They stress the failure, except in a few cases, to demonstrate the acid-fast organism in the lesion. Those who favor the theory that the lesion is tuberculous point to Kyle's investigations as indispensable, if one is to understand the conditions under which the lesion is brought about. It was Kyle's<sup>7</sup> concept that the sarcoid is a distinct type of foreign body reaction to the bacillus of tuberculosis and its disintegration products. He attributed the difficulty of finding the tubercle bacillus in sections of the sarcoid and following its inoculation into animals to the fact that the bacillus is of low virulence and the allergy in such cases rather high. Kyle's microscopic studies are illuminating. Within the first ten days, the changes caused by the invasion of the skin by the bacillus of tuberculosis consisted of a simple inflammation and the presence of numerous tubercle bacilli in the infiltrate. At the end of twenty-one days, endothelial cells made their appearance and became encapsulated. At the same time, the tubercle bacilli gradually began to diminish in number. After thirty-six days, the tubercle bacilli could not be demonstrated microscopically, but the histologic picture described first by Boeck and considered by him characteristic of the disease was noted by Kyle. Other investigators who were able to show the presence of tubercle bacilli in early lesions were Wende<sup>8</sup> and Ruete.<sup>9</sup>

The inadequacy of the assumption of Kuznitzky and Bittorf and Reschin that Boeck's sarcoid is a disease entity is made obvious by the studies of Kyle, Schamnon, Lutz, Bank, Block, Jungling, Jans, Lewandowsky and Goeckerman.<sup>4</sup> These investigators are several among many who found systemic lesions either in lungs or bones (fibrocysts) or in some other anatomic structure of their patients. The presence of tuberculosis in many of the patients and the microscopic and clinical resemblance of the sarcoid to tuberculosis were considered by them as conclusive evidence that the cause of Boeck's sarcoid is tuberculosis, and therefore they could not regard it as a disease entity.

*Syphilis as a Cause*—Most studies of the etiology of Boeck's sarcoid are concerned with the presence of a concomitant tuberculosis. As

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7 Kyle, J. Die Anfangsstadien des Boeckschen Lupoids, Beitrag zur Frage der tuberkulösen Aetiologie dieser Dermatose, Arch f Dermat u Syph **131** 33, 1921

8 Wende G W. Nodular Tuberculosis of the Hypoderm, J Cutan Dis **29** 1 1911

9 Ruete, A. Zur Aetiologie der Boeckschen Erkrankung, Dermat Ztschr **37** 129 1922-1923

a result, the possible presence of systemic lesions is often overlooked Frost's<sup>10</sup> third patient is a case in point. The patient had lesions of the skin on one of her fingers. A roentgenogram of the chest showed increased prominence of the lung markings, leading from the hilum to an area in the upper lobe of the left lung. In this area there were a few discrete patches of increased density from about 0.5 to 1 cm. in diameter. The author assumed that these discrete patches of increased density were evidence possibly of active tuberculosis. It is generally accepted that maturation or infiltration of the lungs beginning at the roots and spreading toward the bases or upward, and associated with clear apexes, is not common in tuberculosis, but is consistent with syphilis, and from the clinical observations and the study of the literature by one of us (D. M. S.) it was found that when patchy, discrete infiltrations of the lungs are associated with Boeck's sarcoid, they are sarcoid lesions.

Notwithstanding the allusion to tuberculosis as a single cause, we believe, nevertheless, that syphilis shares in the causative responsibility for some of the cases. As in tuberculosis, so in syphilis, the organisms can be found in early lesions, but seldom, if ever, in late lesions. Furthermore, *Treponema pallidum* and the tubercle bacillus have one point in common, namely, that they produce multiform lesions which may resemble one another. The tuberculosyphilitic resembles tuberculosis of the skin microscopically and clinically. Evolution of the lesion, which is a tuberculous infiltration of the true skin with gummatous material, is by circumferential growth of new tubercles. Those first formed disappear, leaving scars without previously ulcerating. The syphilitic is maintained by the successive outcrop of new tubercles and a single patch may thus be prolonged for years. If one accepts Kyrle's explanation of the cause of sarcoid by the tubercle bacillus and its disintegration products as a distinct type of foreign body reaction then it must be conceded that *Treponema pallidum* possesses the same potentialities under similar favorable conditions. The following facts indicate that our patient had syphilis and not tuberculosis. In the latter disease there is often considerable involvement of the lungs without dyspnea, but in syphilis of the lungs, dyspnea is a prominent symptom. The productive cough and the expectoration, which, at times, was tinged with blood, would indicate chronic pulmonary tuberculosis. Yet repeated examinations of the sputum revealed no tubercle bacilli. Incidentally, the bloody sputum was caused by bronchial lesions, which were represented by small hemorrhagic patches, and the excruciating abdominal pain and constipation were due to ulcers of the overlying mucosa of

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<sup>10</sup> Frost, K. P. Sarcoid of Boeck, Arch. Dermat. & Syph. **13** 389 (March) 1926.

the intestines. The evidences of syphilis in our patient, to which we attach most weight, were the strongly positive Wassermann reaction obtained with both the blood and the pleural fluid, the areas of perivascular and perineural mononuclear infiltration and the independent collections of mononuclear cells in the liver and elsewhere.

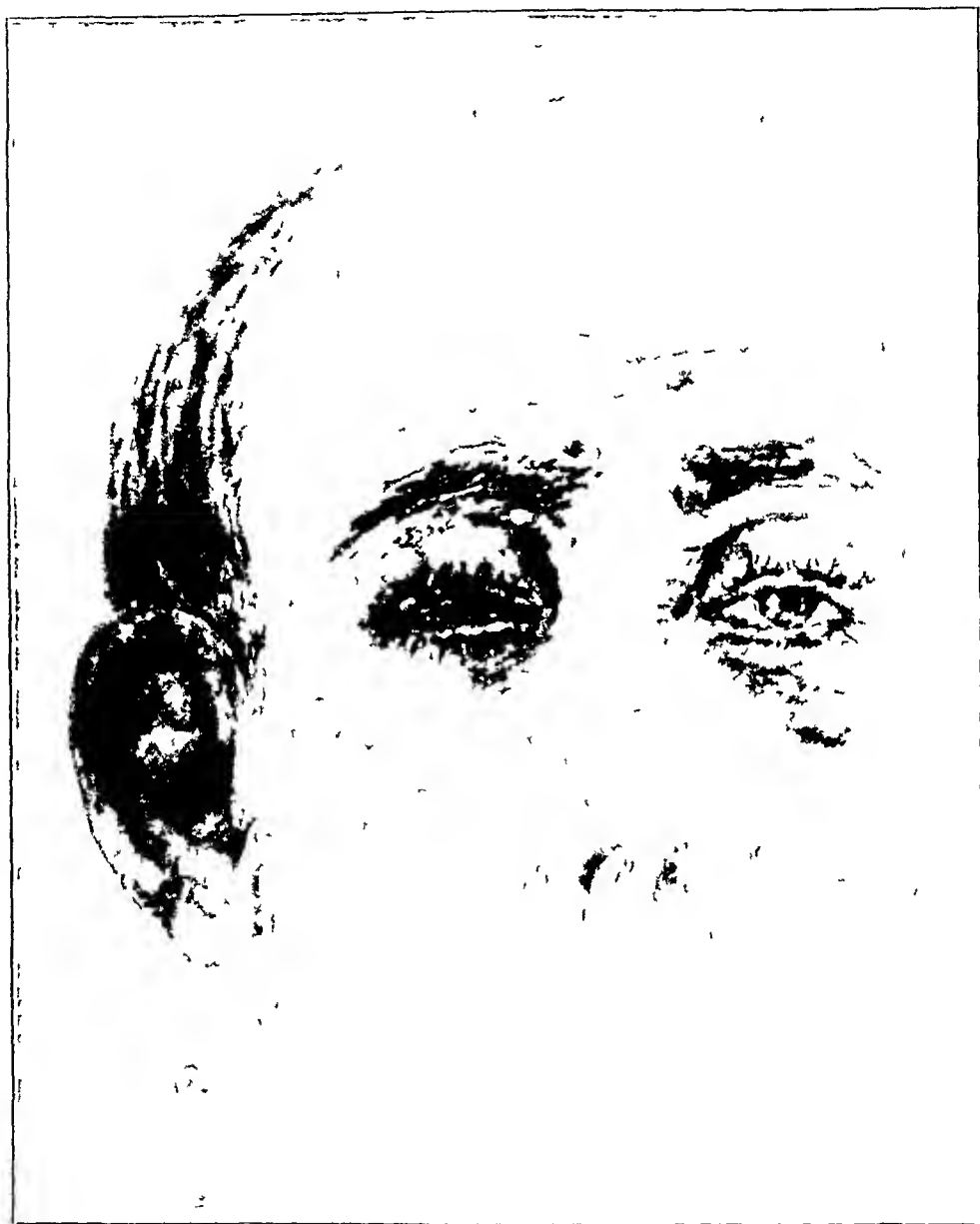


Fig 1—Boeck's sarcoid appearing in the ear, on the eyelid and on other parts of the face

#### REPORT OF CASE

A white man, aged 52, a Russian Jew by birth and a tailor by occupation, was first seen by one of us (M B) in June, 1926. At that time, he complained of weakness and of the presence of purplish lesions, which had appeared two months before, in the ears, on the eyelids and other parts of the face and on the trunk. A marked cyanosis of the lips and the face suggested a possible polycythemia, but



as the red cell count was normal, this diagnosis was discarded. When the patient was seen two months later, he had grown considerably weaker, and a productive cough and expectoration that at times was tinged with blood had developed. He was also dyspneic. The cutaneous lesions were more numerous and consisted of infiltrated plaques, papules and nodules. The lesions were firm and elastic and

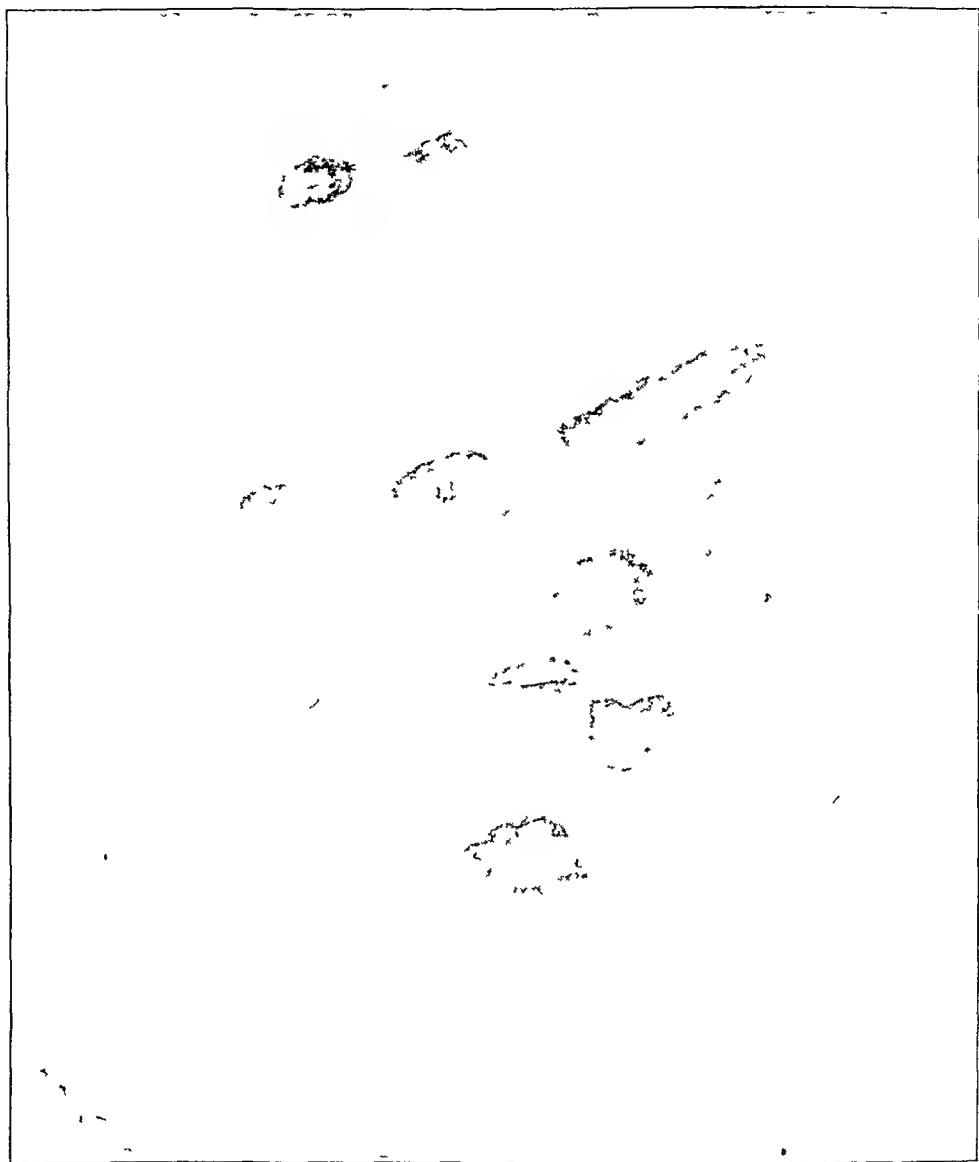


Fig 2—Boeck's sarcoid appearing on the body as plaques, papules and nodules, firm, elastic and purplish

were purplish. Some of these lesions had a reddish tint and presented a delicate central telangiectasis. None of the lesions showed any tendency toward ulceration. The diagnosis of Boeck's sarcoid was made. A section from one of the lesions was excised, prepared and stained in the usual manner for microscopic study. The microscopic sections showed the presence of sharply circumscribed, deep seated nodules, which were separated from one another by connective tissue

septums. The cells comprised epithelioid cells with faintly staining nuclei, lymphocytic plasma cells and a few giant cells.

The examination of the chest revealed signs of a bilateral hydrothorax, which extended to the fifth rib posteriorly on the right side and to the sixth rib posteriorly on the left side. Roentgen examination confirmed the presence of the bilateral hydrothorax, otherwise the report was negative.

The patient's dyspnea became rapidly worse and the pleural fluid was aspirated. In the course of three months, the chest was tapped twelve times: seven times on the right side, for a total of 4,585 cc of pleural fluid, and five times on the left, for a total of 4,945 cc of fluid. The fluid was dark yellow and on several

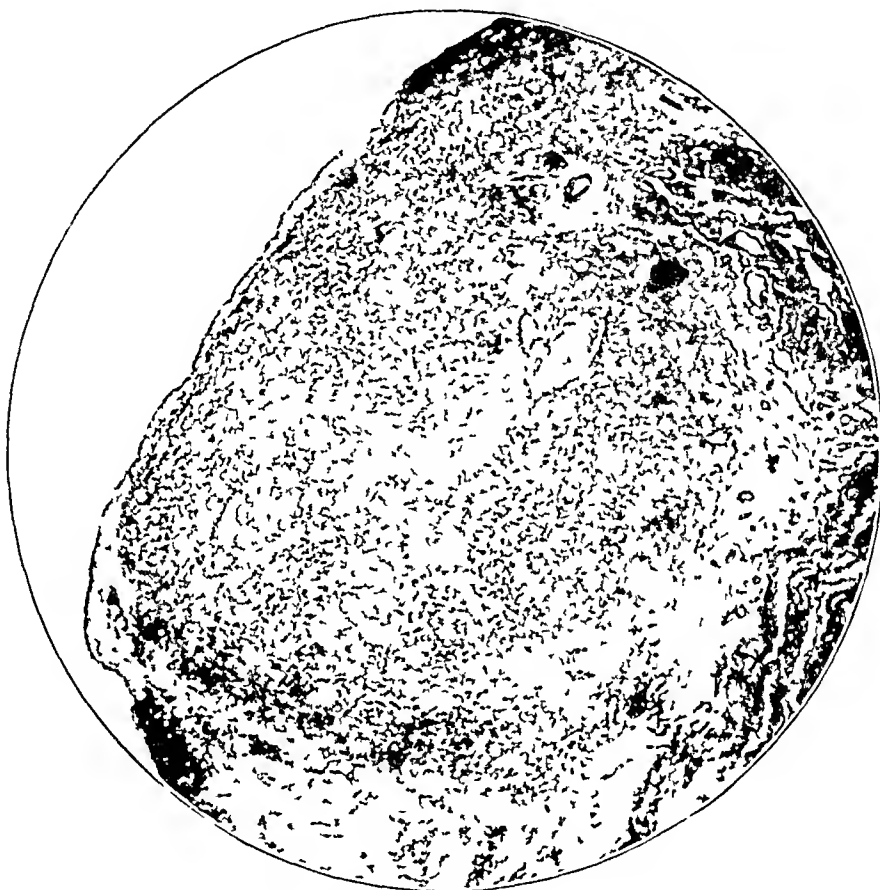


Fig. 3—The nodule as it appeared in the epicardium.

occasions was bloody. Its specific gravity varied between 1.010 and 1.016. It was odorless and sterile on culture. The cell count showed 795 cells per cubic millimeter, of which the polymorphonuclear cells constituted 13 per cent, the small lymphocytic cells 71 per cent, the endothelial cells 6 per cent and the large mononuclear cells 10 per cent. Some of the fluid was injected intraperitoneally into a guinea-pig, but evidence of tuberculosis could not be found three months later. The Wassermann reaction of the pleural fluid was strongly positive.

Repeated examinations of the patient's sputum for tubercle bacilli, spirilla and fungi revealed none. The chemical analysis of the blood showed nonprotein nitrogen 37.2 mg, uric acid 6.2 mg, creatinine 1 mg and sugar 101 mg per hundred cubic centimeters. The Wassermann reaction of the blood was plus 3. The blood pressure was 100 systolic and 80 diastolic. The blood count showed

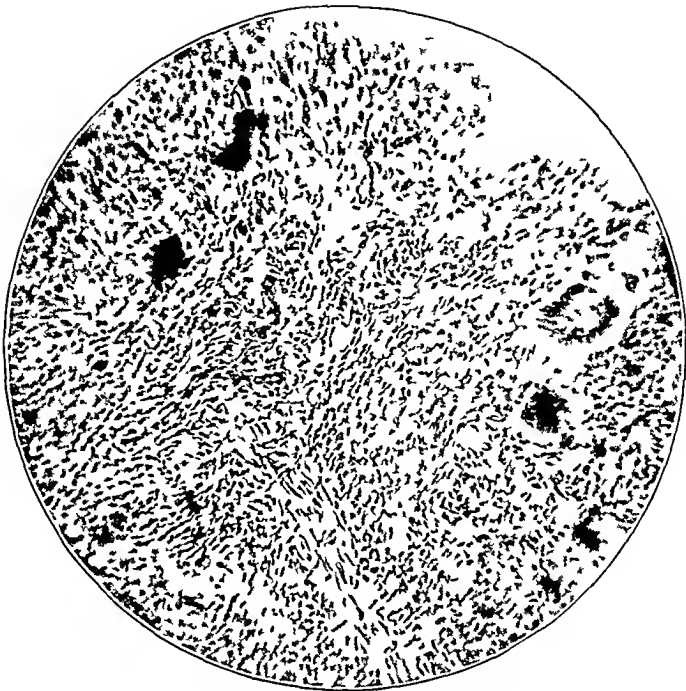


Fig 4—The lesion in the intestine, showing disorderly interlacing bundles of spindle cells



Fig 5—The periphery of the intestinal lesion, showing pigment deposit

hemoglobin content 78 per cent, red cells 5,000,000 and white cells 12,400. The differential count showed polymorphonuclear cells 58 per cent, large lymphocytic cells 35 per cent, small lymphocytic cells 6 per cent and eosinophilic cells 1 per cent. The urine was acid in reaction. The specific gravity was 1.020. A faint trace of albumin, a few hyaline casts and calcium oxalate crystals were reported present. The patient was treated with neoarsphenamine and bismuth, and later with gold sodium thiosulphate, but without any therapeutic effect on the lesions of the skin. The patient grew progressively weaker and died of bronchopneumonia. During the last eight weeks of his life, he suffered from severe, unexplainable abdominal pains and marked constipation.

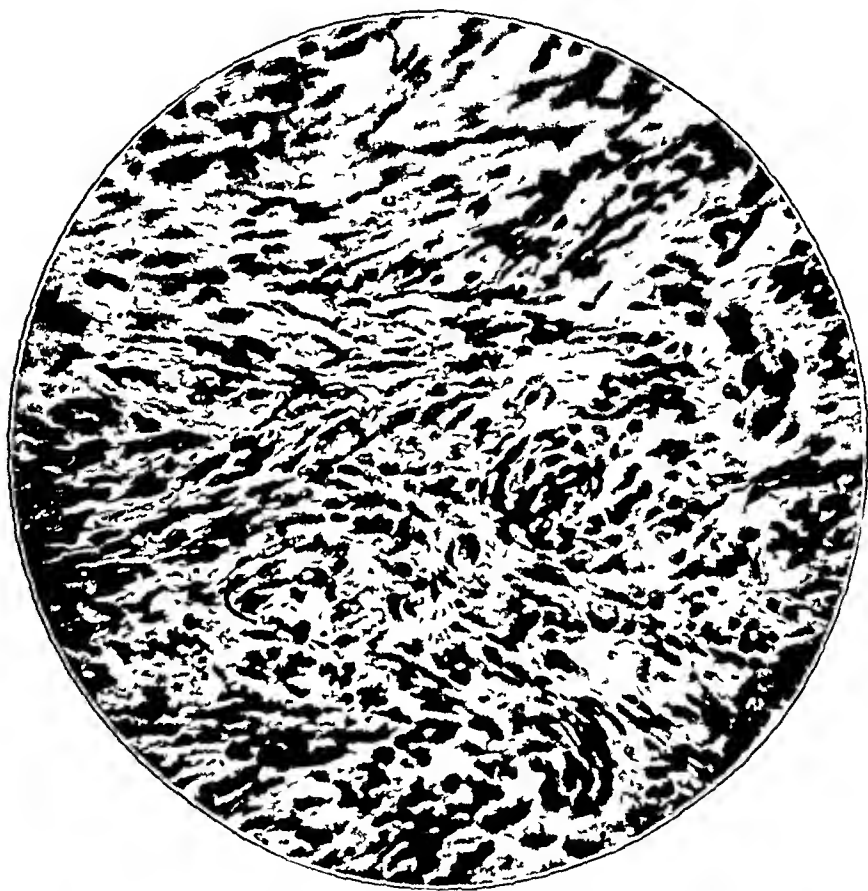


Fig 6—The intestinal lesion, showing type of cell and newly formed capillaries

*Postmortem Examination*—Lesions similar to those of the skin were found in the epicardium, the bronchial mucosa and the mucosa of the ileum.

In the epicardium, they were situated along the course of the coronary vessels, especially the coronary sinus. The nodules there were elongated, dark red and hard, and when incised resembled an organizing blood clot. The superficial muscle fibers were invaded for a distance of 4 or 5 mm. The bronchial lesion was represented by small hemorrhagic patches. In the intestine, the process was marked by thickening of the wall. The serous surface was mottled red, slightly opaque and lacking in luster. The overlying mucosa showed an ulcer 2 by 4 cm in diameter, the floor of which was dark red and necrotic and the edges of which were elevated and indurated. There were many of these ulcers along the course of the ileum.

*Microscopic Examination*—Low magnification emphasized the nodular character of the process. The cellular arrangement varied. In the centers of some nodules, apparently the younger ones, there were many large endothelial spaces filled with red blood cells and much free hemorrhage. Mononuclear leukocytes, plasma cells and eosinophils might be seen in abundance. Near the periphery were newly formed branching capillaries. The vascular endothelial cells were large and stained deeply, and the lumen was broad. Between the capillaries were a few small mononuclear cells and many large elongated cells, some of which behaved like fibroblasts and some of which resembled the endothelial leukocyte of Mallory. These spindle cells formed bundles, which interlaced in a disorderly manner. At

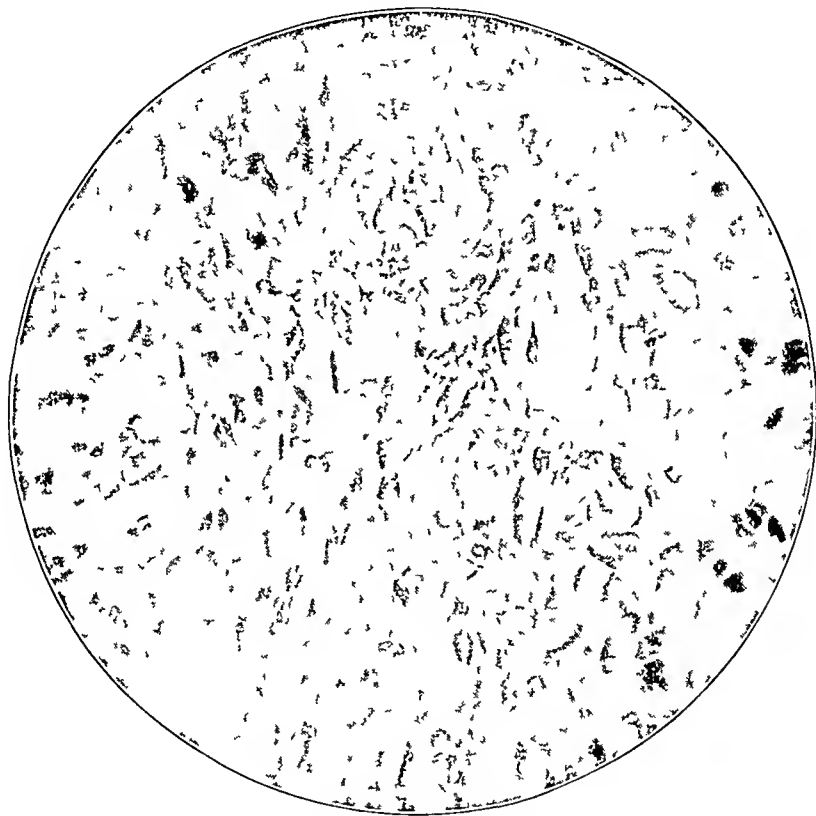


Fig 7—A section showing the type of cell and the intercellular hyaline connective tissue

another stage, the hemorrhagic center was not seen, prominent capillaries embedded in entangled, interlacing bundles of spindle cells formed the entire nodule, the latter sometimes subdivided it into smaller secondary nodules. Large mononuclear leukocytes (so-called epithelioid cells or endothelial leukocytes) lay between the bundles and the capillaries. In the periphery, an abundant brownish pigment was found, most but not all of which became blue when treated with potassium ferrocyanide. At still another stage, hyalinization occurred. It is most peculiar that thick hyaline walls developed even in these newly formed capillaries. The hyaline material was deposited outside the endothelium as a ring or within the lumen, nearly or completely obliterating it. Hyaline material infiltrated, so it seemed, the intercapillary spaces, displacing the many cells seen in other stages. A stage that we take to be final was represented by a homogeneous structure, or

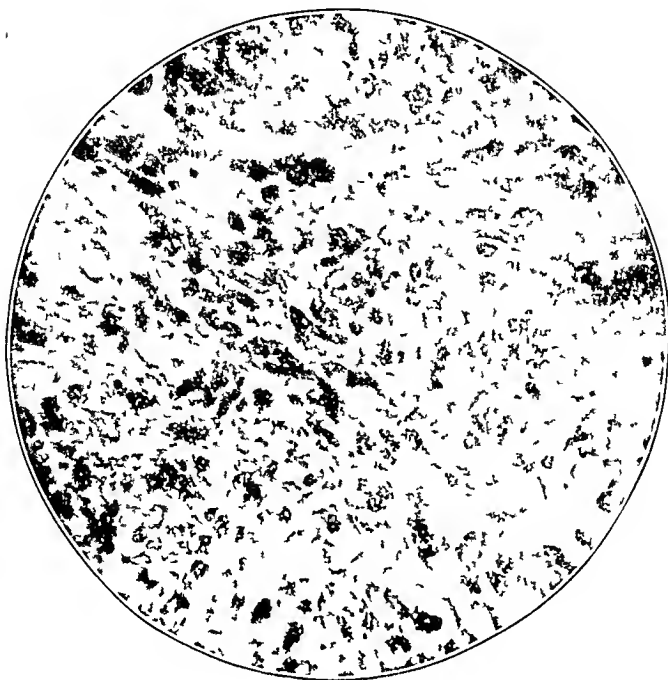


Fig 8—The intestinal lesion, showing newly formed capillaries and hemorrhage

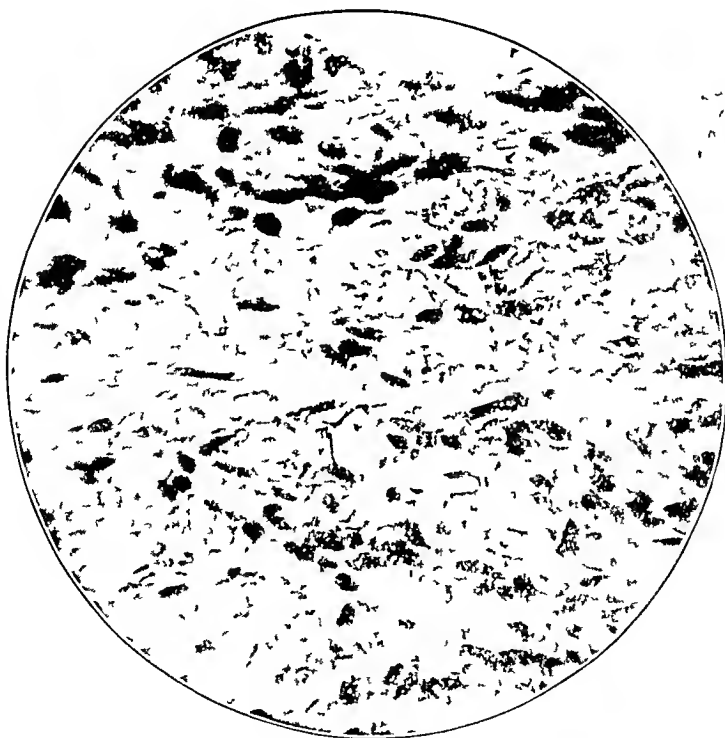


Fig 9—The intestinal lesion, showing hemorrhage

one made up of coarse, wavy fibrils, between which there were spindle cells, much brown pigment and sometimes much hemorrhage

We are inclined to look on the lesion as progressing in stages in the order in which they have been given, but it is far from certain that such is always the case

The lesions of the skin showed less hemorrhage, but were, in general, like those of other parts of the body. Those of the pericardium seemed most typical. In the intestine, they seemed to have started in the submucosa and extended into the mucosa, causing ulceration secondarily. The underlying serosa was thickened and hyalinized. Yet, in these sections, the musculature was intact, so that the process in the serosa was not directly a part of the one seen in the submucosa, but



Fig 10—The intestinal lesion, showing sclerosis and occlusion of capillaries in the periphery

probably an older one. It is our opinion that the lesion appeared in the bronchiole extension from an origin in the adventitia of an associated arteriole. The process here was the same as elsewhere.

We noted with interest collections of small mononuclear cells in the sheaths of nerves of the epicardium and in the adventitia of arterioles not the seat of a definite lesion like that described. Similar collections were also found independent of nerves or arterioles, in the heart, lungs, kidneys and liver.

Bacterial cultures of the tissues were not made, but sections stained for bacteria (including the tubercle bacillus) revealed none. Bacteria of many forms were seen in the intestinal ulcer superficially, but not deep in the lesion, therefore, we assumed these to be secondary invaders of a devitalized tissue. Sections were also examined for *Treponema pallidum* but none was found.

Other lesions found at autopsy and confirmed by microscopic study were bronchopneumonia, chronic aortitis, splenic congestion, fibrosis of the splenic capsule and moderate renal sclerosis

#### COMMENT

It is reasonable to assume from our study that neither the existence nor the significance of the syndrome is as yet appreciated by internists. It is not possible to state the frequency with which the syndrome occurs. But from the perusal of the literature and from the observation of patients with this condition at clinics and at dermatologic clinical conferences, it is evident that the malady is not uncommon. The reasons for

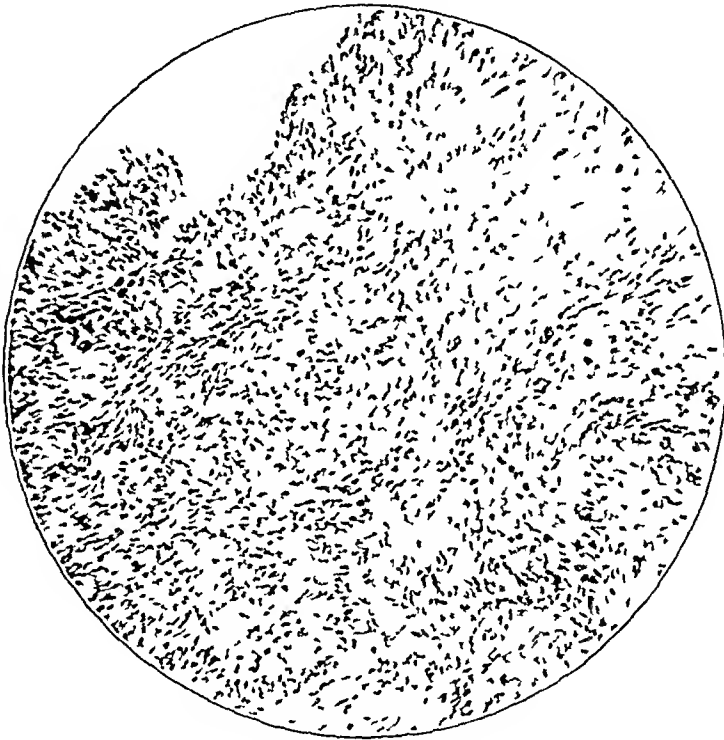


Fig 11—The lesion in the bronchus

the infrequency of reports of patients having systemic lesions are various. We already have had occasion to refer to an instance, and undoubtedly there are many more, in which systemic lesions of Boeck's sarcoid had been confused with tuberculosis. In the past, the cutaneous lesions absorbed all the interest and the systemic lesions were not suspected, consequently, no search was made for them. Then, again, it is not possible, at times, to determine the presence of lesions elsewhere without the aid of a postmortem examination. A good example of this is had in the case of our patient. Incidentally, there is, at the time of writing, a second patient in the hospital with definite sarcoid lesions. The patient's history and the Wassermann reaction of the blood suggest syphilis, but the conditions in the chest are suggestive of chronic tuber-



culosis Yet repeated examinations of the sputum for tubercle bacilli reveal none It is clear that Boeck's sarcoid invades organs and tissues, it is the cause of a syndrome that may resemble one of a number of chronic diseases The resemblance to chronic pulmonary tuberculosis is striking, as illustrated by the patient under observation at this hospital at the time of writing, as well as by the patient reported herein Clinically, Boeck's sarcoid cannot be mistaken for any other condition, and its presence on the skin should instantly suggest the syndrome in a patient whose chest or abdominal condition cannot answer the requirements of known chronic diseases

#### SUMMARY

The lesion described occurs as hard nodules or a group of nodules in the skin, and in the mucous and serous membranes, frequently near or in the adventitia of a small blood vessel The nodule is characterized grossly by a red or bluish red, which does not disappear on pressure, but which, in time, may fade to a red brown Studied microscopically, the nodule is found in various stages At first, it is hemorrhagic and is infiltrated by mononuclear cells Capillaries appear in the periphery and extend inward followed by spindle cells and large mononuclear leukocytes The spindle cells form entangled interlacing bundles and with the mononuclear leukocytes and newly formed capillaries occupy the entire nodule Hyalinization transforms the cellular structure to a relatively acellular homogeneous one containing much iron pigment and a few thick-walled vessels

Areas of perivascular and perineural mononuclear infiltration and independent collections of mononuclears, as seen in the liver and elsewhere, are manifestations of syphilis, which the positive Wassermann reaction suggests

If one bears in mind that Boeck's sarcoid is not limited to the skin but may occur in the viscera, the diagnosis of Boeck's sarcoid syndrome must be given consideration as one of the possibilities in a patient who is suffering from a chronic ailment

#### CONCLUSION

Boeck's sarcoid is an inflammatory, chronic, infectious granuloma The rational etiologic attitude to assume toward this condition is that it is caused by syphilis as well as by tuberculosis

# MALIGNANT LESIONS OF THE GALLBLADDER<sup>\*</sup>

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This report is based on a clinical and pathologic study of fifty-six operatively removed specimens of malignant gallbladders. Microscopic sections were made and stained with hematoxylin and eosin, the corresponding case histories were studied and comparisons were made. The series does not comprise the total number of malignant lesions of the gallbladder removed at the Mayo Clinic but only those specimens available and suitable for study. The records of the pathologic museum show that 14,978 gallbladders removed at operation were sent to the museum between 1910 and 1927, and that 89 of these were malignant.

## INCIDENCE

The incidence of malignancy of the gallbladder is commonly given as ranging from 0.5 to 5 per cent. Murphy,<sup>1</sup> in one of his clinics, stated that carcinoma of the gallbladder is a rare disease. W. J. Mayo,<sup>2</sup> in an earlier report on 405 operations performed on the gallbladder and biliary passages for all causes, found that 5 per cent were for malignant disease. Smithies,<sup>3</sup> in a report of twenty-three proved instances of the disease, gave the percentage as 2.3. Erdmann,<sup>4</sup> in a series of 224 cases, found a percentage of 6.7, and observed that the occurrence of malignant lesions of the gallbladder was about 6 per cent of that of all malignant lesions. In his series the number of malignant lesions specified in various organs were: gallbladder fifteen, stomach forty-three, breast sixty-six, colon and sigmoid twenty-eight, rectum and rectosigmoid twenty-nine, cecum twelve, and not specially classified seventy-nine (including malignant lesions of the uterus, kidney, tongue, liver and thyroid gland). MacCarty,<sup>5</sup> in 1919, published a survey of 4,998

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<sup>\*</sup> Submitted for publication, June 21, 1929.

1 Murphy, J. B. Carcinoma of Cholelithic Gallbladder, Exploratory Celiotomy, *Surg. Clin.* **5**: 427, 1916.

2 Mayo, W. J. Malignant Disease Involving the Gallbladder, *Med. News* **81**: 1105, 1902.

3 Smithies, F. Primary Carcinoma of the Gallbladder. An Analysis of Twenty-Three Proved Instances of the Disease, *Am. J. M. Sc.* **157**: 67, 1919.

4 Erdmann, J. F. Incidence of Malignancy in Disease of the Gallbladder, *Am. J. Obst.* **80**: 618, 1919.

5 MacCarty, W. C. The Frequency of the "Strawberry" Gallbladders, *Ann. Surg.* **69**: 131, 1919.

gallbladders removed at operation, in that series there were 24 cases of carcinoma, or about 0.5 per cent

At the Mayo Clinic the relative frequency of malignancy of the gallbladder has diminished from an average of about 5 per cent in earlier years to about 0.5 per cent in later years. In 1910 there were 4 carcinomas in 165 cases in which cholecystectomy was performed, and in 1928 there were 5 carcinomas in 1,094 cases, the difference in percentage is undoubtedly due to the fact that diseased gallbladders are now removed earlier.

#### AGE AND SEX

The ages of the patients having malignant lesions of the gallbladder varied from 39 to 77 years. Carcinoma of the gallbladder is extremely rare before the age of 50 years. It is practically unheard of in the twenties, but Proescher<sup>6</sup> reported malignancy of the gallbladder in the case of a man aged 22. Although malignancy of the gallbladder may occur at any time in middle age, it manifests itself chiefly in the fifth and sixth decades, 74 per cent occurring between the ages of 50 and 60. Given in half decades, there was one patient between 35 and 40 years of age, one between 40 and 45, four between 45 and 50, twelve between 50 and 55, fifteen between 55 and 60, thirteen between 60 and 65, five between 65 and 70, two between 70 and 75, and three between 75 and 80.

It is commonly reported that women are affected with malignant disease of the gallbladder three times as commonly as men. Siegert<sup>7</sup> found seventy-nine women to fourteen men. W. J. Mayo found about the same proportion. Erdmann's cases were all those of women. In this series there were forty-four women and twelve men, supporting the common contention of the 3:1 proportion. All but five of the women had been pregnant one or more times.

#### CLINICAL DATA

It is commonly believed that the symptoms of malignancy of the gallbladder are mostly silent, being chiefly those of the milder types of dyspepsia of the gallbladder. Although this is true in some instances, most patients have a history which is at least suggestive. Patients with malignant lesions of the gallbladder may roughly be placed in three groups. The first group, comprising about 70 per cent, has a history of repeated attacks of colic of the gallbladder over a period of from several to many years, followed by a change in symptoms designating the malignant phase, which is usually of from three to six months'.

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6 Proescher, Frederick. A Remarkable Case of Carcinoma of the Gallbladder in a Man Twenty-Two Years Old, *J. A. M. A.* 48:481 (Feb. 9) 1907.

7 Siegert, quoted by Mayo (footnote 2).

duration This terminal stage of disease of the gallbladder is characterized by constant pain in the epigastrium or right upper quadrant of the abdomen, vomiting, profound anorexia, weakness, and progressive loss of weight of from 15 to 30 pounds (6.8 to 13.6 Kg.) in from three to six months. The second group, comprising about 22 per cent, has symptoms of an apparently harmless condition of the gallbladder, such as intolerance for food, gastric distress after eating, belching, constipation, sour eructations and a minimal amount of pain and tenderness over the area of the gallbladder, not associated with weakness, loss of weight or loss of appetite. The third group, or about 9 per cent, has apparently not been conscious of any disease of the gallbladder prior to a terminal malignant stage, in which there is a fairly sudden onset of pain, progressive loss of weight and marked weakness and anorexia.

Jaundice may be present, depending on encroachment on the biliary duct system or extensive involvement of the liver. Thirteen of the fifty-six patients had jaundice at the time of the examination.

There is usually a fair degree of tenderness in the area of the gallbladder. A mass was palpable in twenty-nine cases (55 per cent), and seven of the patients had felt the tumor themselves.

The gastric acids were available in twenty-three cases. There were only four in which achlorhydria was present, in these cases the average total acidity was 15. In the remaining nineteen cases the average hydrochloric acid was 32, and the average total acidity was 48.

The blood picture in cases of malignant disease of the gallbladder is not that frequently found in cases of malignant disease in other parts of the body, in that anemia is not associated. Only five of the patients in the series reported here had a hemoglobin of less than 70 per cent, and none had a hemoglobin of less than 60 per cent. The average hemoglobin for the entire series was 73 per cent (Dare) which is considered within normal limits at the clinic.

Metastasis may take place in the liver, the adjacent lymph nodes, or the extrahepatic biliary duct system. In 35 per cent of the cases there was extension into the liver and in five of these there was involvement of the regional lymph nodes. Metastasis to regional lymph nodes alone was found in eight cases. In five there was extension into the biliary passages and in one of these the lymph nodes were affected.

Stones were found to be an almost constantly associated factor. In Deaver's<sup>8</sup> experience calculi were found in 89 per cent of cases of carcinoma of the gallbladder. Courvoisier<sup>9</sup> found that in seventy-four of eighty-four cases of malignant disease of the gallbladder, stones

8 Deaver, J. B. Carcinoma of the Gallbladder, *Am. J. Surg.* 38:105, 1924.

9 Courvoisier, quoted by Mayo (footnote 2).



Fig 1—Adenocarcinoma of the gallbladder

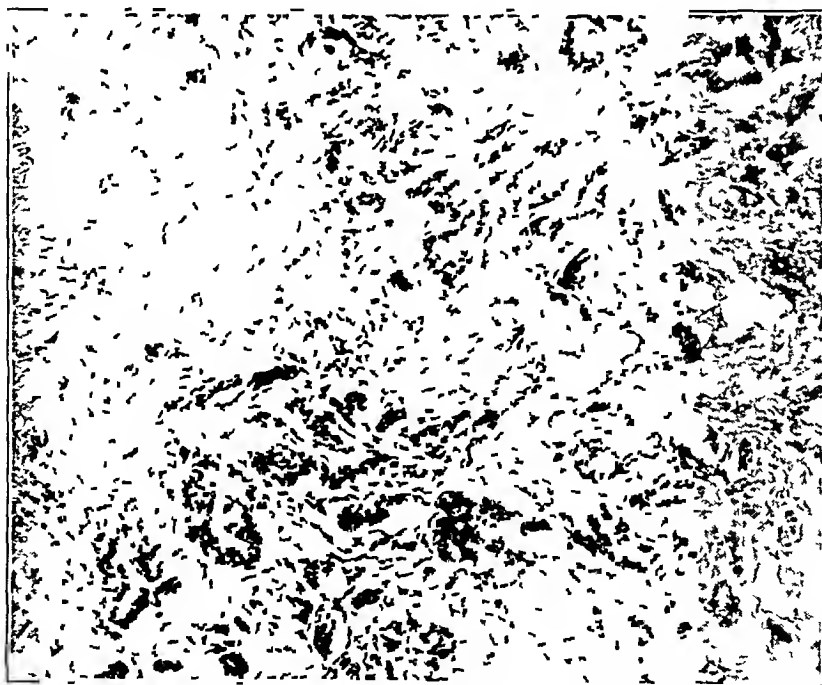


Fig 2—Adenocarcinoma of the gallbladder with acini containing columnar epithelial cells

were present Siegart stated that in cases in which the neoplasm was primary, stones were present in 95 per cent, and in cases in which neoplasm was secondary, stones were present in 15 per cent. In the present series, stones were present in fifty-three cases (94 per cent).

Cholecystectomy only was performed in twenty-nine cases and partial cholecystectomy only in five cases. Cholecystectomy with choledochostomy for relief of obstruction of the common duct was performed in four cases, and in one of these a portion of the common duct was likewise resected. Cholecystostomy only was performed in eight cases. In one case, gastro-enterostomy along with cholecystectomy was necessary because of pyloric obstruction. In seven cases the only surgical



Fig. 3—Gross appearance, squamous cell epithelioma of the gallbladder

procedure was exploratory operation and removal of a specimen for diagnosis. Choledochostomy was performed in one case and jejunostomy in one.

#### POSTOPERATIVE LONGEVITY

No record of longevity was available in nine cases. Webber,<sup>10</sup> in a recent article, graded many of these specimens according to the method of Broders<sup>11</sup> and gave the corresponding duration of life in that paper. Therefore an attempt was not made in this report to compare the grade

10 Webber, I. M. Grades of Malignancy in Primary Carcinoma of Gallbladder, *Surg. Gynec. Obst.* **44**: 756, 1927.

11 Broders, A. C. Carcinoma Grading and Practical Application, *Arch. Path.* **2**: 376 (Sept.) 1926.



Fig 4—Squamous cell epithelioma of the gallbladder containing epithelial pearls



Fig 5—Squamous cell epithelium and adenocarcinoma in the same alveolus

of malignancy with expectancy of life Twelve patients lived one month or less, seven lived two months, three lived four months, three lived five months, two lived six months, three lived seven months, one lived eight months, one lived nine months, one lived less than one year, but the exact date of death was not given, three lived one year, one lived thirteen months, one lived fourteen months, one lived somewhat less than three years, three lived four years, and in one of these cases the family physician reported carcinoma of the liver at necropsy, although this was probably a slow extension from the old malignant lesion of the gallbladder One patient lived seven years and one lived eight years Three patients were alive after fifteen months, eight years, and fourteen years, respectively



Fig 6—Papillary adenocarcinoma of the gallbladder

#### PATHOLOGY

Microscopic sections were made and examined, and graded by Broders according to the method previously described by him

The types of malignancy of the gallbladder in this series are adenocarcinoma, squamous cell epithelioma, papillary carcinoma and sarcoma

Adenocarcinoma occurred most commonly These types consist of branching acini of round or oval cylindric cells, some of these surround a central lumen, and others completely obliterate the lumen There were forty-nine belonging to the adenocarcinoma group (figs 1 and 2) The malignancy in these cases was graded 1 in four cases, 2 in twenty cases, 3 in eleven cases and 4 in fourteen cases

There were three cases of squamous cell epithelioma (figs 3 and 4) These growths contained squamous cells, intracellular fibers and horny cell nests This type of tumor is rare Nicholson,<sup>12</sup> in 1919, reported

12 Nicholson, G W Three Cases of Squamous-Celled Carcinoma of the Gallbladder, *J Path & Bact* **13** 41, 1909



three cases of squamous cell epithelioma of the gallbladder, and sixteen others that he reviewed from the literature. Various theories have been advanced as to the possible causes of this condition, and two that have been suggested apparently deserve serious consideration. 1 It is due to misplaced embryonic tissue probably from an esophageal anlage. 2 It is due to metaplasia, this hypothesis is the more likely.

Metaplasia has been variously defined<sup>13</sup> as the transition of one tissue into another of a related kind, or as the formation of different tissues from a common parent cell. It has been noted in various organs, including the skin, gallbladder, stomach, breast and uterus. Just what

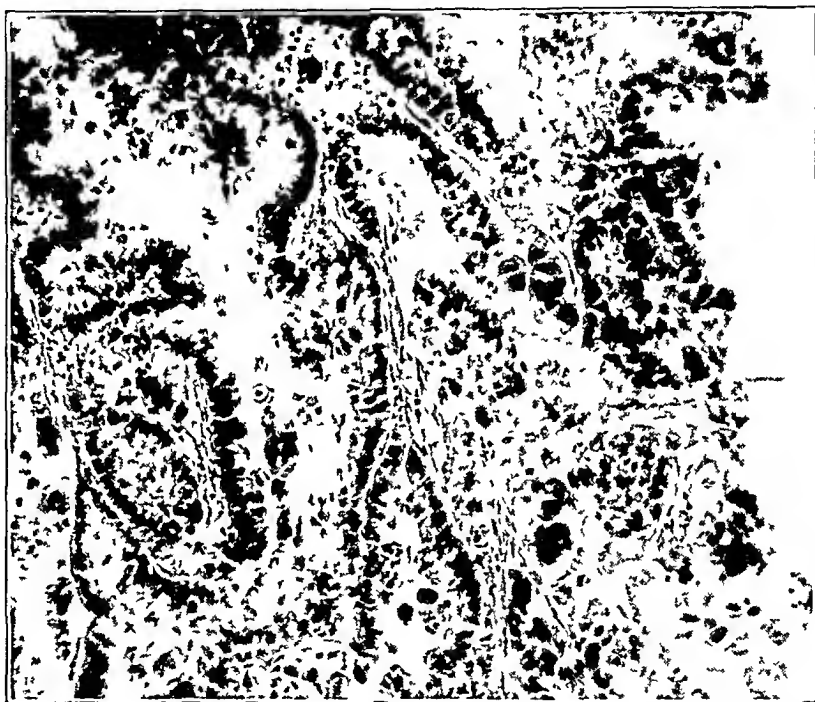


Fig 7—Papillary adenocarcinoma of the gallbladder, illustrating the papillary character of the tumor

initiates the change of one tissue to another of a related kind is not known, but apparently chronic inflammation or irritation is necessary for the process. Futterer<sup>14</sup> has been able to produce metaplasia in the pyloric end of the stomach of rabbits by long-continued irritation. Normally, squamous epithelium does not exist in the gallbladder or in any of the adjacent organs, and so it is only by assuming that these tumors arose partly because of the change of the tissue by metaplasia

13 Caylor, H. D. Practical Considerations of Metaplasia in Neoplastic Diseases, *J. Lab. & Clin. Med.* **13** 714, 1928

14 Futterer, G. Ueber experimentelle Erzeugung von Magengeschwüren und über Schleimhautwucherungen an deren Randern, *Festschr. f. G. E. von Rindfleisch*, 1907, p. 89

that their origin can be explained<sup>15</sup> Of such epitheliomas in this series there was one each of grade 1, 2 and 3, according to Briers' system of grading There were two other specimens, examples of metaplasia, which contained both adenocarcinoma and squamous cell epithelioma graded 2 In one of these tumors (fig 5), adenocarcinoma formed a portion of a single acinus, and squamous cell epithelioma formed the remainder of the same alveolus

There was one case of papillary adenocarcinoma graded 3 (figs 6 and 7) The relationship between papilloma and papillary carcinoma is problematic About 10 per cent of all gallbladders have one or more



Fig 8—Lymphosarcoma of the gallbladder

papillomas, yet papillary carcinoma is relatively rare Hruska<sup>16</sup> and Ringel,<sup>17</sup> however, both reported malignant degeneration in the papillomas

There was one case of lymphosarcoma of the gallbladder, associated with stones (figs 8 and 9) The patient was a woman aged 41 In 1914, Iwasaki<sup>18</sup> reported a case of his own and at that time found

15 Lubarsch, Otto Die Metaplasiefrage und ihre Bedeutung für die Geschwulstlehre, Arb a d path anat Abt d k hyg Inst zu Posen, 1901, p 205

16 Hruska Einen Fall von krebsiger Umwandlung eines Papilloms der Gallenblase, Wien klin Wchnschr 29 1263, 1916

17 Ringel Ueber Papillom der Gallenblase, Arch f klin Chir 59 161, 1899

18 Iwasaki, K Ueber das primäre Sarkom der Gallenblase, Arch f klin Chir 104 84, 1914

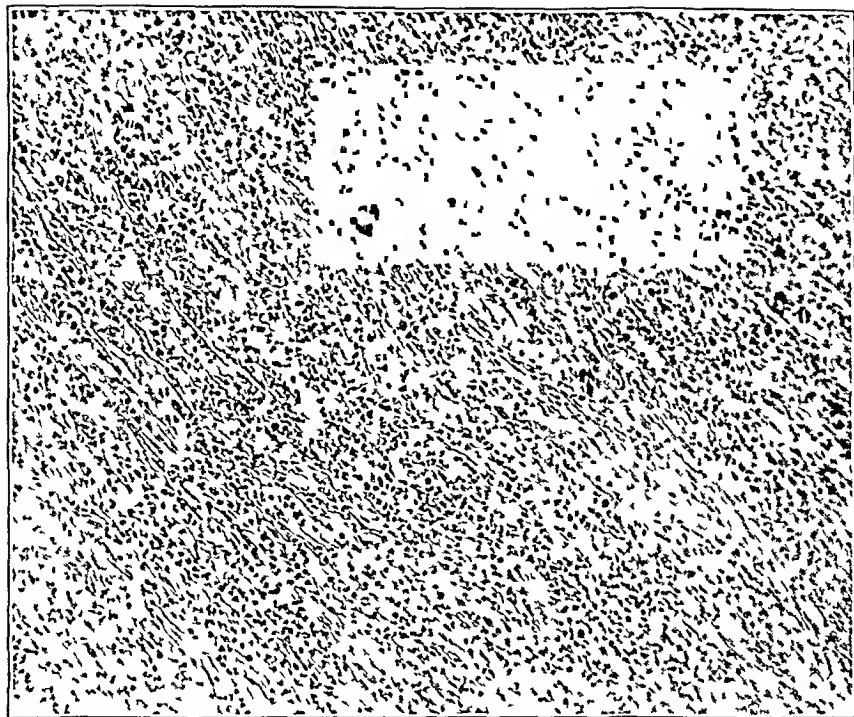


Fig 9—Lymphosarcoma of the gallbladder (low power magnification)

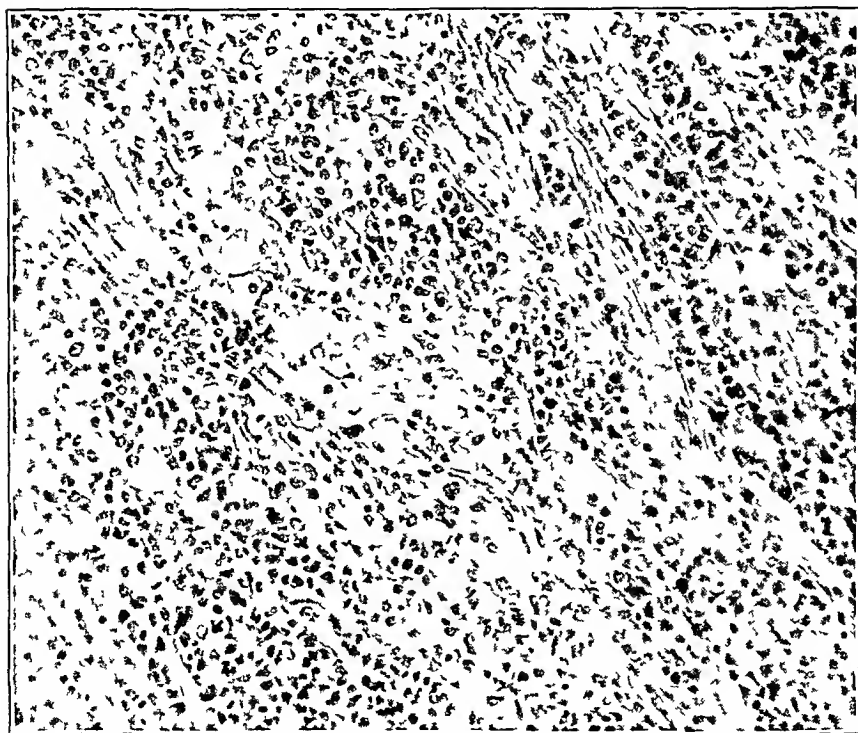


Fig 10—Lymphosarcoma of the gallbladder, illustrating more intimate details of the tumor cells

only eight other cases in the literature Carson and Smith<sup>19</sup> reported a case in 1915, and in 1921 Goldstein<sup>20</sup> was able to find only sixteen cases of primary sarcoma of the gallbladder in the literature

#### SUMMARY

A clinical and pathologic study has been made of fifty-six cases of malignancy of the gallbladder

The incidence of malignancy of the gallbladder is about 0.5 per cent It rarely occurs before the age of 50, and women are affected about three times as commonly as men

Although the symptoms of malignancy of the gallbladder are not definite, about 70 per cent of patients have a long history of repeated gallbladder attacks, followed by a short phase characterized by constant pain, anorexia, vomiting and progressive weakness and loss of weight

There is almost never an associated anemia in malignancy of the gallbladder In about a sixth of the cases there is achlorhydria, and in the remaining cases the average free hydrochloric acidity is 32, and the average total acidity, 48

Stones are an almost constantly associated condition in cases of malignant disease of the gallbladder, 94 per cent of gallbladders having calculi

The types of malignancy of the gallbladder are adenocarcinoma, squamous cell epithelioma and sarcoma Adenocarcinoma occurs most commonly Squamous cell epithelioma occurs as a process of metaplasia, probably from long-continued irritation

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19 Carson, N. B., and Smith, G. M. Primary Sarcoma of the Gallbladder, *Ann. Surg.* **62**: 688, 1915

20 Goldstein, H. I. Primary Sarcoma of the Gallbladder, *Am. J. Surg.* **35**: 351, 1921

# CARCINOMA OF THE RENAL CORTEX WITH FACTORS BEARING ON PROGNOSIS \*

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Carcinoma of the renal cortex presents a complex pathologic problem, so complex that since Grawitz,<sup>1</sup> in 1884, gave the first accurate description of the condition and called attention to the relation of the structure of renal carcinoma to that of the suprarenal gland, observers have constantly been attempting to name the entire group by some embryologic, histologic or other descriptive term

Birch-Hirschfield termed the tumor described by Grawitz "hypernephroma" Adam,<sup>2</sup> on a basis of embryologic development, suggested the term "mesothelioma" Sudeck<sup>3</sup> took exception to associating the tumor described by Grawitz with suprarenal rests, favoring their association with renal adenoma Stoerk<sup>4</sup> supported Sudeck's views and advanced the hypothesis that hypernephroma might arise from proliferations of the adult secreting epithelium of the convoluted tubules Wilson and Willis<sup>5</sup> concluded that there was almost no evidence, embryologic or histologic, in support of Grawitz' hypothesis that so-called hypernephromas have their origin in suprarenal rests, feeling rather that the evidence at hand favored the hypothesis that hypernephromas originate from islands of nephrogenic tissue (primitive renal blastoma) More recently the comprehensive term, nephroma, was suggested to include tumors originating in the kidney At the present time, however, the majority of pathologists are inclined to look on all epithelial tumors of the renal cortex as carcinoma MacCarty,<sup>6</sup> Bro-

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<sup>1</sup> Submitted for publication, June 19, 1929

1 Grawitz, Paul Die Entstehung von Nierentumoren aus Nebennierengewebe, Arch f klin Chir **30** 824, 1884

2 Adam, J G The Principles of Pathology, ed 1, Philadelphia, Lea & Febiger, 1909, p 768, ed 2, 1910, p 807

3 Sudeck, Paul Ueber die Structur der Nierenadenome Ihre Stellung zu den Strumae suprarenals aberratae (Grawitz), Arch f path Anat **133** 405, 1893

4 Stoerk, Oskar Zur Histogenese der Grawitzschen Nierengeschwulste, Beitr z path Anat u z allg Path **43** 393, 1908

5 Wilson, L B, and Willis, B C A Comparative Study of the Histology of the So-Called Hypernephromata and the Embryology of the Nephridial and Adrenal Tissues, J M Research **24** 73, 1911

6 MacCarty, W C Personal communication

deis<sup>7</sup> and Robertson<sup>8</sup> classify them as carcinomas, mostly of renal origin, and believe that the various pathologic features represent different degrees of cellular differentiation

Foulds and Braasch<sup>9</sup> have pointed out that two separate groups of cortical tumors can be demonstrated pathologically and clinically, adenocarcinoma and alveolar carcinoma. Those in the group of adenocarcinoma, or those otherwise known as hypernephroma, are characterized by a higher degree of cellular differentiation than is found in those of the group of alveolar carcinoma in which there is less cellular differentiation. In alveolar carcinoma, in many instances, there are solid cords, without lumens, composed of granular or clear cells. The clinical course of patients with adenocarcinoma is distinct from that of patients with alveolar carcinoma. Possibly some of the discrepancies noted in data concerning such tumors are due to the combination in the same tumor of features of adenocarcinoma and of alveolar carcinoma.

#### MATERIAL

This study comprises a series of 367 cases of carcinoma of the kidney seen at the Mayo Clinic from Jan 1, 1901, to Jan 1, 1928. It includes 225 cases reported by Hunt and Hager<sup>10</sup> in a recent review of 271 cases of malignant neoplasm, seen at the Mayo Clinic between Jan 1, 1918, and Jan 1, 1928. Of the 312 patients who underwent nephrectomy, 283 have been traced. Of the fifty-five patients who were submitted to exploration, only forty-seven have been traced. In all the patients traced, the age, sex, symptoms, pathologic features, operative procedure, supplementary treatment such as that by roentgen ray and radium, metastasis, and associated infection have been considered in order to determine their bearing on the postoperative length of life. In this paper we shall refer to the entire group under the name of renal carcinoma. We shall designate the less malignant group, generally called hypernephroma, as adenocarcinoma, and the more malignant group as alveolar carcinoma.

#### PATHOLOGY

Adenocarcinomas of the kidney are frequently associated with tortuous, dilated superficial veins, these are often ruptured and cause troublesome bleeding during nephrectomy. In fifty-one of those patients who were traced, the renal carcinomas were confined to the upper pole, in sixty, they were limited to the lower pole, in thirty-nine, the

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7 Broders, A. C. Personal communication.

8 Robertson, H. E. Personal communication.

9 Foulds, G. S., and Braasch, W. F. Postoperative Results of Nephrolithiasis, *J. Urol.* **11** 525, 1924.

10 Hunt, V. C., and Hager, B. H. A Review of 271 Cases of Malignant Renal Neoplasms, *S. Clin. N. Amer.* **9** 149, 1929.

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lesions were in the midrenal region, in ten, the entire kidney was involved, and in 123 the involvement was in combinations of the regions mentioned. In 104 patients, the renal capsule was broken through by the carcinoma, and the perirenal tissues were involved. Extension had occurred into the renal veins (fig 1) in fifty-one cases. Metastasis was observed in ninety-eight instances.

In advanced and fatal cases, carcinomas become large, destroying most of the kidney and undergoing necrosis and hemorrhagic and cystic softening. Extension occurs by continuity through the kidney. The renal pelvis is often encroached on, or the ureteropelvic juncture is obstructed and hydronephrosis results.

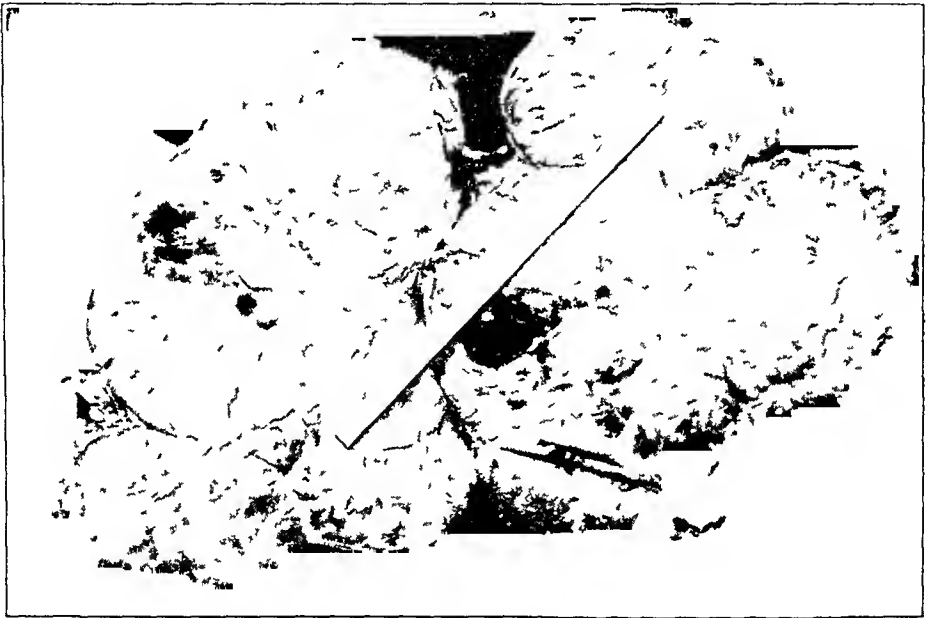


Fig 1—Carcinoma of the kidney, graded 4, with extension into the pelvis and veins, associated hydronephrosis, destruction of practically all of the renal substance. A woman, aged 52 years, had had hematuria ten years and again five months before operation. She first noticed tumor in the right upper quadrant of the abdomen about five months before operation. Nephrectomy was performed Oct 15, 1925. The patient is now living and well.

In some specimens the histologic structure presents definite tubules closely resembling a renal tubule and lined by dark, granular cells, in others, the structure is the same, but the cells are clear. In the majority of these carcinomas there is a cystic papillary structure (figs 2 and 3) without distinct tubules and with clear (fig 4) or granular cells. In other carcinomas the structure is one of solid cords (alveolar) without lumens and with granular or clear cells. Occasionally the microscopic picture consists of darkly staining cells arranged loosely, like a round cell sarcoma. Two or more of these types of tissue are



Fig 2—Typical structure of papillary adenocarcinoma,  $\times 60$

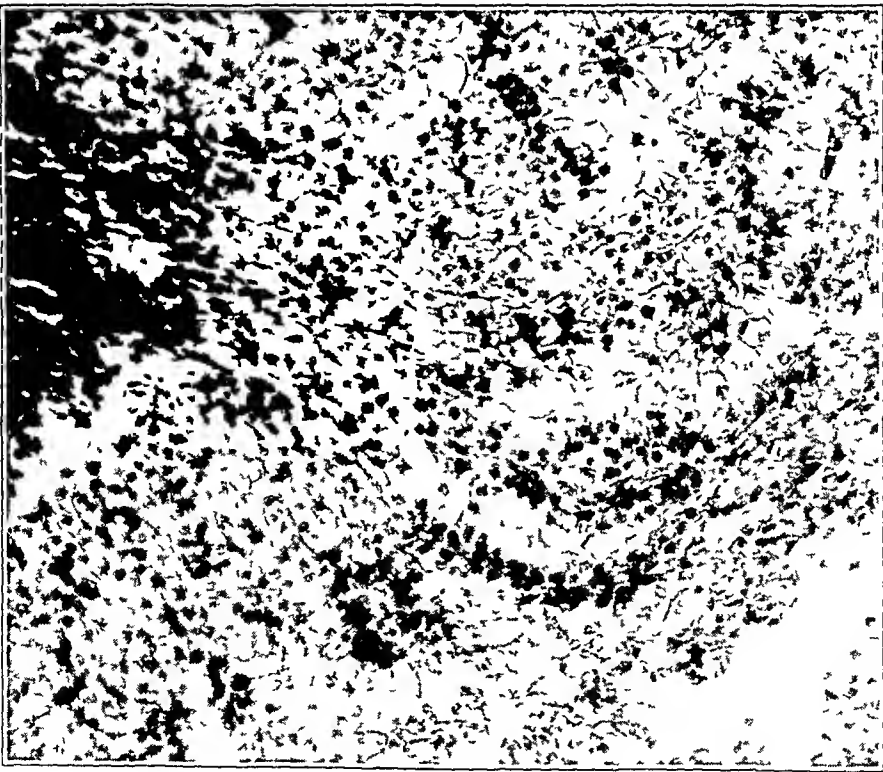


Fig 3—Papillary adenocarcinoma,  $\times 120$

often presented in different parts of the same carcinoma. It is possible that a few of the alveolar carcinomas may arise from supra-renal rests, but there is no convincing evidence of this origin. Alveolar carcinomas are less common than carcinomas of the papillary type. In the patients who underwent nephrectomy or exploration and who were traced, the proportion of alveolar carcinoma to adenocarcinoma was 43:287.

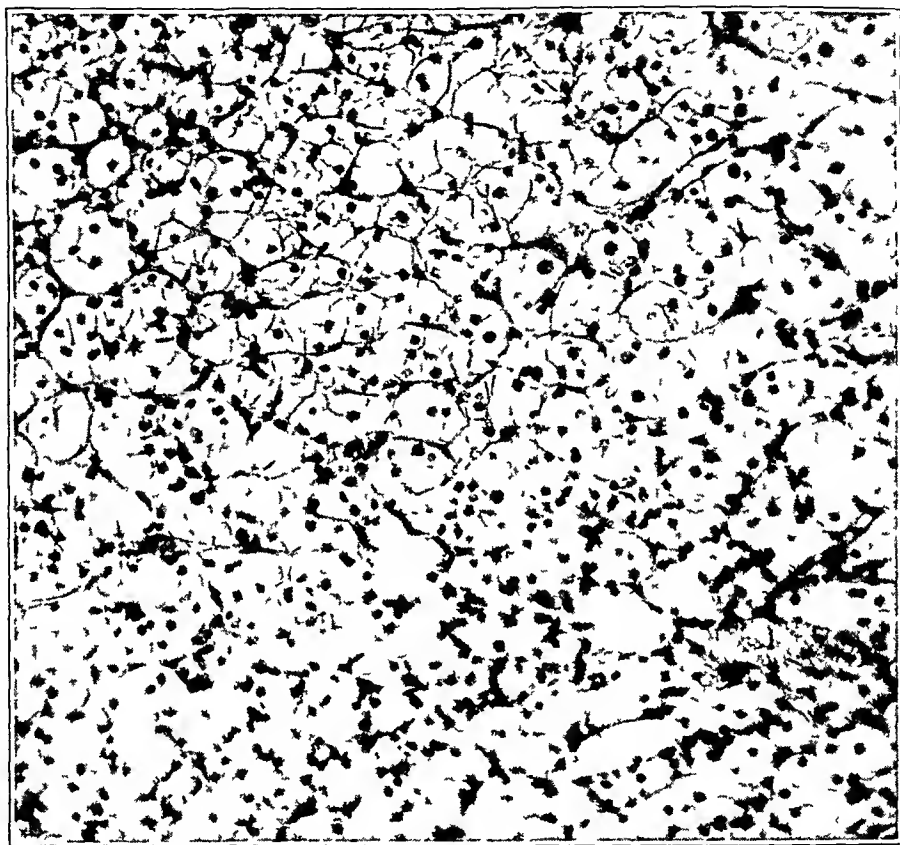


Fig. 4—Clear, undifferentiated, foamy appearing cells, usually recognized as characteristic of hypernephroma,  $\times 200$ . According to terminology in this paper the tumor would be called a clear-celled papillary carcinoma. There was almost complete destruction of the renal substance in this case. The patient lived four and a half years after operation.

The lesion involved the right kidney in 169 cases (46.04 per cent) of the series, and the left kidney in 196 cases (53.40 per cent). In two instances the side involved was not stated. Our records show that twenty-six of the 283 patients who underwent nephrectomy and who were traced lived ten years or more, in fifteen of these, the carcinoma involved the right kidney (57.67 per cent), and in eleven the left kidney (42.31 per cent).

## RELATION OF AGE TO ONSET OF SYMPTOMS AND POSTOPERATIVE LENGTH OF LIFE IN RENAL CARCINOMA

In this series of 367 patients, the average age was 51.76 years. The age at which the first symptom appeared and the time that elapsed before surgical operation was undertaken had a direct bearing on longevity. One hundred sixty-one patients had the first symptom before the age of 50, in 203, the first symptom appeared after the age of 50, and in three the age was not recorded. In 63 per cent the first symptom occurred between the ages of 40 and 60 years, whereas in 37 per cent it appeared between the ages of 50 and 60 years.

In the group of patients who underwent nephrectomy, those who were living Jan. 1, 1929, had acquired symptoms earlier in life and had come to operation earlier than those who died. In 192 patients who underwent nephrectomy and who are dead, the average age at which the first symptom appeared was 50.56 years, the average age at operation was 52 years and 6 months, and the average duration of postoperative life was 28 months. In ninety-one patients who underwent nephrectomy and who still are living, the average age at which the first symptom appeared was 47.01 years, the average age at operation was 50.47 years and the average duration of postoperative life thus far is 80 months (6.65 years).

In the group of forty-seven patients who underwent exploration and who were traced, forty-five are dead. In these the average age at which the first symptom occurred corresponds with the average age at onset in the group in which nephrectomy was done, that is, 50.84 years. However, a long period elapsed between the time of appearance of the first symptom and the time when these patients came to operation. The average age at operation was 53.11 years. The average duration of postoperative life was 1.72 years. In the two patients living at present the symptoms appeared earlier, at the average age of 35 years and 6 months. Here again, the time when the patients came to operation was delayed, the average age at operation was 41 years. The patients have lived an average postoperative life of 29.5 months. In the cases in which exploration alone was possible, a surgical procedure was not undertaken as soon after the onset of symptoms as in the group in which nephrectomy was done.

## RELATION OF SEX TO POSTOPERATIVE LENGTH OF LIFE IN RENAL CARCINOMA

Of the 367 patients, 116 were women, and their average age was 50.45 years, 251 were men, and their average age was 52.36 years.

Of the 283 patients who underwent nephrectomy and who were traced, 191 (67 per cent) were men. Of these, 132 are dead, their average postoperative life was 29.12 months. Fifty-nine men are living

and have thus far lived 81.11 months. Ninety-two (32 per cent) of the patients who underwent nephrectomy were women. Sixty are dead, having lived an average postoperative life of 26.48 months. Thirty-two of these ninety-two patients are living and have had an average postoperative life of 79.68 months. The average duration of symptoms before operation in the 191 men was 28.14 months and in the ninety-two women, 26.64 months. The average duration of symptoms and the average postoperative duration of life, both of patients who are dead and of patients who still are living, are less for women than for men. This suggests that possibly renal carcinoma runs a more rapid course in women.

Of the forty-seven patients who underwent exploration and who have been traced, thirty-eight (80 per cent) were men, of whom thirty-six are dead after an average postoperative life of 22.38 months. The two others have been living now for an average postoperative life of 29.05 months. Nine of these patients (19 per cent) were women. Of these, all are dead, after an average postoperative life of 11.41 months. In this group of forty-seven patients who were subjected to exploration only and who have been traced, the average duration of symptoms before operation for the men was 35 months, and for the women, 9.5 months. From these data it will be noted that in the group of patients who underwent nephrectomy and in the patients who were submitted to exploration, the average duration of symptoms and the average length of postoperative life were much less for women than for men. That the average duration of symptoms is less for women may be explained by their noting symptoms and receiving surgical attention sooner than men, that in spite of this, they should have a shorter average postoperative life than men, again suggests that in women the malignant process may possibly run a more rapid course. In the two sexes, the relation of exploration to nephrectomy can be expressed approximately by the following ratios: men, one operation of exploration to five of nephrectomy, and women, one of exploration to ten of nephrectomy. That the proportion of inoperable carcinoma is less in women than it is in men is probably due again to their seeking surgical assistance before the malignant process became locally extensive.

RELATION OF THE DURATION OF SYMPTOMS BEFORE OPERATION  
TO POSTOPERATIVE LENGTH OF LIFE IN ADENOCARCINOMA  
AND ALVEOLAR CARCINOMA

The average duration of symptoms before operation was longer in patients subjected to nephrectomy for adenocarcinoma than in those in whom nephrectomy was done for alveolar carcinoma. In the 192 patients on whom nephrectomy was performed, and who died subse-

quently, the average duration of symptoms before operation was 21.73 months for those who had adenocarcinoma and 17.43 months for the corresponding group with alveolar carcinoma. In the ninety-one patients on whom nephrectomy was performed and who still are living, the average duration of symptoms was 40.97 months for the group with adenocarcinoma and 32.5 months for the corresponding group of patients with alveolar carcinoma. From these data it will be seen that in the patients on whom nephrectomy was possible, symptoms were present for a longer time in the group with adenocarcinoma than in the group with alveolar carcinoma.

In forty-seven patients who were traced, the extent of the pathologic process permitted only of an exploration. The average duration of symptoms was much longer in these patients than for those in the group in which nephrectomy was done, this stresses the importance of earlier operation after the advent of symptoms, if nephrectomy is to be possible. In the patients now dead who were submitted for exploration and whose conditions were diagnosed as alveolar carcinoma, the average duration of symptoms was 41.5 months, this is twenty-four months more than the average duration of symptoms in the group with alveolar carcinoma in whom nephrectomy was possible. In those patients who have died in whose cases the diagnosis was adenocarcinoma and exploration alone was possible, the average duration of symptoms was 25.37 months. This is an average of four months longer than the average duration of symptoms in the group with adenocarcinoma in whom nephrectomy was performed.

In the deceased patients who were subjected to exploration and whose conditions were diagnosed as adenocarcinoma, the average postoperative length of life was 21.72 months, whereas in those patients whose conditions were diagnosed as alveolar carcinoma, the average postoperative length of life was 15.85 months.

Of the forty-seven patients who were submitted to exploration and who have been traced, only two are living. In both of these the diagnosis was adenocarcinoma. The average duration of symptoms was 62.5 months and the average postoperative length of life thus far has been 29.5 months. It may be seen from these data that the postoperative course of patients with alveolar carcinoma tends to a more rapidly fatal issue than that of the patients with adenocarcinoma.

#### FREQUENCY OF SYMPTOMS

Pain was present at some time as a symptom in 307 of the 367 cases (83.65 per cent). Hematuria occurred at some time in 253 cases (68.93 per cent). A tumor was noted in 291 cases (79.29 per cent). Weakness occurred in twenty-nine cases (7.90 per cent). There was absence of

a history of urinary disorder in eight cases (2.17 per cent) and absence of a history of illness in two (0.54 per cent)

#### TUMOR

The presence of a tumor was noted by patients in fifty-one (13.89 per cent) of the 367 cases, however, a tumor was demonstrated on general examination in 291 of the cases (72.29 per cent). The following data emphasize that as the tumor becomes large enough to be palpable and finally becomes fixed, the mortality rate is increased. Death occurred in thirty-three of sixty-five cases in which a mass was not palpable and in seventeen of thirty cases in which a mass was palpable and in which mention was not made of mobility or fixation. In ninety of the cases a movable mass was recorded, sixty-one of the patients are dead, and twenty-nine are living. In nine cases the mass was definitely recorded as fixed, in eight of these death occurred. The relation of a large mass to mortality is well demonstrated in the forty-seven cases in which exploration only was carried out, and which were traced, a fixed, and in many cases an infiltrating, tumor was noted in forty-four cases. Death has occurred in forty-two of these forty-four cases.

#### THE SITUATION OF THE CARCINOMA IN THE KIDNEY IN RELATION TO MORTALITY AND POSTOPERATIVE LENGTH OF LIFE

The carcinoma was situated in the upper pole of the kidney in fifty-one instances, in the lower pole in sixty instances, and it occupied the midrenal region (figs 5 and 6) in thirty-nine instances. In ten instances, the entire kidney was involved. The involvement was not well defined in 123 kidneys. Sixty-six per cent of the patients in whom the involvement was noted in the upper pole of the kidney are dead, 64 per cent of those in whom the growth was in the lower pole also are dead as well as 55 per cent of those in whom the midrenal region was involved.

The patients who still are living, in whom the upper pole of the kidney was involved, have lived a longer average postoperative life than those in whom involvement of the lower pole and midrenal region was noted. The average postoperative length of life in patients still living is 129.46 months for those patients in whom the upper pole of the kidney was involved, as compared with 83.30 months for those with involvement of the lower pole of the kidney, and 76.92 months for those with involvement of the midrenal region. In the patients who died the relation of the situation of the tumor to the postoperative length of life is not so striking. The average postoperative length of life is 40.44 months for those patients in whom the upper pole of the kidney was involved, as compared with 38.09 months for those with involvement of the lower pole of the kidney, and with 39.05 months for those with

involvement of the midrenal region Tumors of the lower pole of the kidney may interfere with renal drainage, favoring the development of a variable degree of hydronephrosis and infection

#### SIZE OF THE CARCINOMA WITH RELATION TO POSTOPERATIVE LENGTH OF LIFE

The size of the carcinoma bears a rather distinct relationship to the mortality rate In 161 cases in which nephrectomy was performed the



Fig 5—Papillary carcinoma arising from practically the entire convex surface of the kidney The patient was a man, aged 59 years, who had a mass in the left upper quadrant of the abdomen for two years He died on the eleventh post-operative day, infection was a contributing cause

carcinomas were recorded as large, death occurred in 129 In eighty-two cases the carcinomas were moderate in size, fifty of the patients are dead and thirty-two are living In thirty-six cases the carcinomas were recorded as small, ten of the patients are dead and twenty-six are living In four cases the size of the tumor was not stated The patients who had small carcinomas and died lived a much longer postoperative length of life than the patients who had moderate-sized tumors



Carcinomas were recorded as large in thirty-six of the cases in which exploration was performed. Thirty-five of the patients are dead. In eleven cases in which exploration was carried out the size of the carcinoma was not stated.

#### HEMOGLOBIN IN RELATION TO MORTALITY

In spite of any other factor, death occurred in 75 per cent of sixty-three cases in which the hemoglobin was less than 60 per cent,

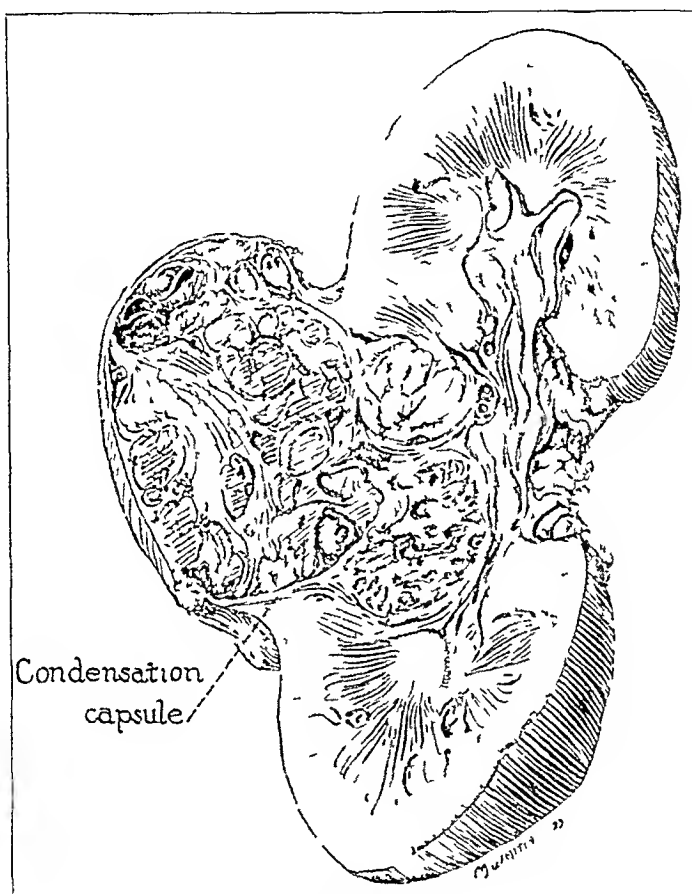


Fig 6—Adenocarcinoma involving the middle portion of the left kidney, the lesion is encapsulated. The patient was a man 45 years of age, who had had intermittent attacks of pain and hematuria for five weeks. He is living and well eleven years after nephrectomy.

whereas death occurred in 60 per cent of the 171 cases in which the hemoglobin was recorded as being more than 60 per cent. Further, of 118 cases in which the hemoglobin was less than 70 per cent, death occurred in 76 per cent and in 51 per cent of 116 cases in which the hemoglobin was more than 70 per cent. Thus it will be seen that a direct relationship seems to exist between the hemoglobin at the time of nephrectomy and subsequent mortality.

# INVOLVEMENT OF RENAL VEINS

There was extension to the renal veins in fifty-one of the cases in which nephrectomy was done, there have been forty-two deaths, and among these nine deaths in the hospital. In 231 cases, extension to the renal veins was not noted, there were 151 deaths, and among these twenty-one deaths in the hospital. The average postoperative length of life in those patients with involvement of the renal veins who are dead was 24.46 months, the corresponding figure for those patients who were without involvement of the renal veins was 24.37 months. Among the patients who are living, those patients in whom there was involvement of the renal veins had an average postoperative length of life of 72.77 months, whereas the average postoperative length of life for patients still living in whom the renal veins were not involved was 82.09 months. A greater percentage of patients are dead in the group with involvement of the renal veins than in the group without such involvement, metastasis and subsequent pyelophlebitis played major parts as contributory causes of death. Extension to the renal veins greatly increases the difficulty of accurate hemostasis. The veins become rigid and friable and lose their elasticity. After ligation or clamping of the pedicle the contained plug of tissue prevents accurate healing of the incised veins. One patient died on the fourth postoperative day from secondary hemorrhage that followed the removal of clamps from the renal pedicle.

# PERIRENAL INVOLVEMENT

In 104 of the cases in which nephrectomy was performed and which were traced, the perirenal tissues were involved, or the capsule was broken through (fig 7). There have been eighty-four deaths, twelve of which occurred in the hospital, in the other seventy-two cases in which death occurred, the average postoperative life was 17.23 months. In twenty cases of this group, the patients have been living now for an average of 77.2 months. No doubt in some of the cases in which the patients have lived so long the fixation of the tumor noted at the time of operation was the result of inflammatory reaction rather than malignant attachment. Perirenal involvement was not noted in 179 cases. Death occurred in 108 of these, in eighteen of which death occurred in the hospital, and in ninety of which the average postoperative life was 37.22 months. In seventy-one cases in which perirenal involvement was not noted, the average postoperative length of life thus far is 81.15 months. It will be noted here that a much lower mortality rate exists in the cases in which perirenal involvement did not occur. In eighty-four cases the perirenal tissues were involved or the capsule was found broken. In twenty-three of these, there was metastasis, and in thirteen there was local recurrence of the carcinoma. Of the twenty cases in

which the patients are living in which perirenal involvement was noted at operation, metastasis has been reported in only one, and local recurrence in two. This emphasizes the fact that local recurrence and metastasis play major parts as factors in mortality.

Twenty-six patients are dead of the group of twenty-seven of those who underwent exploration and in whom the perirenal tissues were evidently involved or the capsules broken. In this group six instances of metastasis were noted. Metastasis was present in the case of the patient who is still living after exploration in which the perirenal tissue was found to be involved.

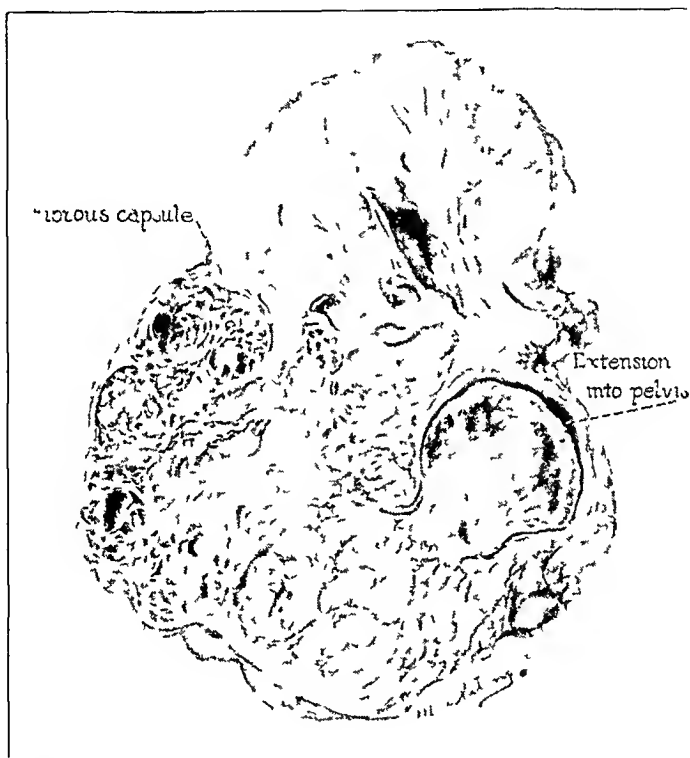


Fig. 7—Papillary carcinoma 10 by 8 by 6 cm which had perforated the capsule and projected into the pelvis. The patient was a man, aged 40 years. He gave a history of pain in his back and intermittent hematuria for fourteen months. He lived five years and ten months following right nephrectomy.

The total number of cases in which nephrectomy or exploration was performed and in which the perirenal tissues were found to be involved or the capsules broken was 131 (tables 1 and 2), in thirty-one of these (23.66 per cent) there was metastasis, and in fifteen (11.45 per cent) there was local recurrence. However, in sixty-seven (33.66 per cent) of the 199 cases in which perirenal involvement did not occur or in which the capsule was not broken, there was metastasis, and in thirty-six (18.09 per cent) there was recurrence. The higher percentage of recurrences and metastasis which occurred in the cases without

perineal involvement would seem to indicate that the gross pathologic condition is not an exact criterion as to whether or not extension has occurred

# OPERATIVE PROCEDURE IN RELATION TO MORTALITY AND POST- OPERATIVE LENGTH OF LIFE

*Incision*—In the 283 cases in which nephrectomy was performed and which were traced, the surgical approach was made through a posterior

TABLE 1—*Record of 312 Patients of Whom 283 Were Traced Who Had Adenocarcinoma or Alveolar Carcinoma of the Kidney and Who Underwent Nephrectomy Between Jan 1, 1901, and Jan 1, 1928*

	Deaths (192)				Patients Living (91)	
	Cases	Hospital Deaths	Subsequent Deaths	Average Postoperative Life, Months	Cases	Average Postoperative Life, Months
Males	132	24	108	29 12	59	81 11
Females	60	6	54	26 48	32	79 68
Right	86	15	71	33 59	47	84 61
Left	106	15	91	22 60	44	76 81
Posterior incision	125	18	107	28 88	71	76 88
Anterior incision	63	11	52	25 92	18	100 66
Anterior and posterior incisions					2	33 00
Type of incision not stated	4	1	3	37 00		
Movable tumor	61	10	51	22 34	29	74 68
Fixed tumor	8	1	7	26 75	1	98 00
Palpable tumor	73	17	56	27 28	16	87 25
Kidney palpable	17		17	34 62	13	61 53
No palpable tumor	33	2	31	36 07	32	88 93
Lesion in lower pole	40	4	36	38 09	20	85 30
Lesion in upper pole	36	7	29	40 44	15	129 46
Lesion median in position	23	3	20	39 05	16	76 92
Lesion involved entire kidney	8	3	5	50 20	2	37 00
Situation of lesion indeterminate	85	13	72	14 18	38	62 73
Tumor large	129	24	105	23 37	32	87 53
Tumor moderate sized	50	6	44	25 67	32	78 68
Tumor small	10		10	43 20	26	75 96
Size not stated	3		3	7 0	1	53 00
Extension into renal vein	42	9	33	26 46	9	72 77
No extension into renal vein	150	21	129	24 37	82	82 09
Perirenal tissue involved or capsule broken	84	12	72	17 23	20	77 20
No involvement	108	18	90	37 22	71	81 15
Forceps on pedicle	25	7	18	22 33	5	85 6
Ligation of pedicle	167	23	144	28 79	86	79 97
Roentgen ray alone	51		51	24 37	27	46 03
Roentgen ray and radium	12		12	35 09		
Radium alone	8	1	7	10 57	1	96 00
No radiologic treatment	121	29	92	30 61	63	95 12
Carcinoma	25	5	20	16 86	8	37 00
Hypernephroma	167	25	142	29 67	83	84 77

incision in 196 (69 25 per cent), through an anterior incision in eighty-one (28 62 per cent), and through an anterior and a posterior incision in two cases (70 per cent). In the other four cases (1 41 per cent) the type of incision was not stated

In the cases in which exploration was performed, posterior incision was used in fourteen cases (29 78 per cent), and an anterior incision, in twenty-nine (61 70 per cent). The type of incision was not stated in four cases (8 51 per cent). In the cases in which exploration was performed, an anterior incision was used in 61 70 per cent, whereas in

cases in which nephrectomy was performed an anterior incision was used in only 28.62 per cent. Because of the greater risk in the anterior incision and also because of technical improvements in the posterior incision, the posterior incision has been used in nearly all cases in the last few years.

*Pedicle Controlled by Forceps or Ligature*—In thirty cases, nearly 10 per cent of the total number in which nephrectomy was performed, it was deemed advisable to allow forceps to remain on the vascular pedicle.

TABLE 2—*Record of Fifty-Five Patients, of Whom Forty-Seven Were Traced, Who Had Adenocarcinoma or Alveolar Carcinoma of the Kidney and Who Underwent Exploration Between Jan 1, 1901, and Jan 1, 1928*

	Deaths (45)				Patients Living (2)	
	Cases	Hospital Deaths	Subsequent Deaths	Average Postoperative Life, Months	Cases	Average Postoperative Life, Months
Males	36	4	32	22.88	2	29.5
Females	9		9	11.41		
Right	16	2	14	18.25	1	28.0
Left	29	2	27	21.76	1	31.0
Posterior incision	12	3	9	12.11	2	29.50
Anterior incision	29	1	28	14.29		
Anterior and posterior incisions						
Type of incision not stated	4			77.75		
Movable tumor	11		11	20.45	1	31.00
Fixed tumor	5	1	4	5.87	1	28.00
Palpable tumor	22	3	19	17.20		
Kidney palpable	4		4	6.50		
No palpable tumor	3		3	76.60		
Lesion in lower pole	3		3	13.30		
Lesion in upper pole	1		1			
Lesion involved entire kidney	1		1	6.0		
Lesion median in position						
Situation of lesion indeterminate	40	4	36	21.72	2	29.50
Tumor large	35	2	33	19.0	1	31.00
Tumor moderate sized						
Tumor small						
Size not stated	10	2	8	26.37	1	28.00
Extension into renal vein	4		4	4.62		
No extension into renal vein	41		41	14.03	2	29.50
Perirenal tissue involved or capsule broken	26	3	23	13.47	1	31.00
No involvement	19	1	18	29.96	1	28.00
Roentgen ray alone	7		7	16.85	1	31.00
Roentgen ray and radium	6		6	13.83		
Radium alone	1	1			1	28.00
No radiologic treatment	31	3	28	28.95		
Carcinoma	10	2	8	15.85		
Hypernephroma	35	2	33	21.72	2	29.50

for from seventy-two to ninety-six hours, rather than to attempt ligation. Twenty-five of the patients are dead, seven of whom died in the hospital, hemorrhage was an associated factor in three of these seven deaths in the hospital. One patient died from hemorrhage on the day of operation, another, in whom there was a questionable degree of bleeding, died of shock. A third patient died on the fourth postoperative day and death was attributable to secondary hemorrhage. Two patients died of sepsis. One patient died on the fifteenth postoperative day, bronchopneumonia and pleurisy were found at necropsy. Another patient died on the first postoperative day following right nephrectomy. In this instance the

pleura on the right side was accidentally opened and immediately sutured at the time of nephrectomy. At necropsy the right lung was found to be collapsed, and in addition a moderate degree of pleurisy with effusion was present. The average postoperative life in cases in which forceps were allowed to remain on the vascular pedicle was 22.33 months. Five patients have thus far lived an average postoperative life of 85.6 months. This compares favorably with the results in the group of 253 cases in which the vascular pedicle was tied, 167 of the patients are dead, twenty-three of whom died in the hospital and 144, subsequently. The latter patients had an average postoperative life of 28.79 months. Eighty-six per cent of the patients in whom the vascular pedicle was tied had an average postoperative life of 79.97 months.

*Nephrectomy and Primary Ureterectomy*—In twelve cases in which nephrectomy was performed, the primary operation involved treatment of the ureter. In ten of these cases, it was necessary to perform nephrectomy and partial ureterectomy. In one case, nephrectomy and ureterectomy were performed, in another, nephrectomy and ureterectomy were done, the ureterectomy including the portion of the ureter that is intramural in the bladder. One of these patients returned later and another operation was done for recurrence. Four of these twelve patients are dead, after having lived, respectively, three, eight, eleven and forty-six months, an average length of life of seventeen months. Seven patients are living, one of these patients has lived seven months, two patients, one year, and the remaining four patients, four years and five months, seven years, nine years and five months, and eight years, respectively. One patient in this group of twelve was not traced.

*Nephrectomy and Subsequent Ureterectomy*—Following nephrectomy three patients returned, and subsequent ureterectomy was performed. One patient returned because of gross hematuria associated with typical, severe renal colic, symptoms which developed ten months following nephrectomy. Another patient had profuse, gross hematuria that occurred at practically every micturition, this did not develop, however, until five years after the nephrectomy. Three months following nephrectomy, a third patient suffered from severe lower abdominal pain associated with gross hematuria and the passing of small pieces of tissue at each micturition. One of these patients underwent partial ureterectomy, and the microscopic sections showed the adenocarcinoma to have infiltrated the ureteral wall. This patient lived one year and five months following the second operation. In another patient, ureterectomy was performed, at operation the ureter was found embedded in a mass of recurrent adenocarcinoma, the patient lived one year. The third patient, who required ureterectomy, gave an interesting subsequent history. Microscopic sections of the ureter revealed adenocarcinoma. Shortly after ureterectomy, symptoms developed suggestive of tumor of

the brain. At exploration a specimen was removed from the lesion in the brain and was diagnosed as metastatic carcinoma. The patient lived five years and four months following the nephrectomy.

Judging from this experience, it is doubtful whether removal of the entire ureter at the time of nephrectomy would have offered any better prospects. Probably removal of the upper part of the ureter is indicated and is sufficient in practically all cases of renal carcinoma.



Fig 8—Adenocarcinoma involving lower pole of left kidney, subsequent ureterectomy for recurrence five years following the nephrectomy. The patient died three months after ureterectomy. Interim exploration of a tumor of the brain proved it to be metastatic.

#### RECURRENCE

Definite recurrences were noted in fifty-one cases in which nephrectomy was performed. In six other cases, symptoms and data were present which suggested recurrence. In ten of the fifty-one cases with recurrences the patients returned for surgical procedures. In three cases subsequent ureterectomy was performed (fig 8), and in one additional

case there was involvement of the lower three ribs on the side from which the tumor was removed. In one case exploration was performed, and a duodenal ulcer was found in addition to the local recurrence. Exploration of the wound was performed in two cases, and in three others tissue was removed from the site of operation. At the primary operation in the cases in which recurrences developed later, the capsule was broken through in three cases and the surrounding tissue was involved in one case. Local recurrences were reported in thirty-one (23.65 per cent) of the 131 cases in which perirenal involvement was noted, or the capsule was reported as broken through by the carcinoma at the time of nephrectomy.

#### METASTASIS

That carcinoma of the kidney does not remain a local disease, is attested to by the following data: definite metastasis was noted at necropsy in thirty-one instances, in thirteen it was noted at operation, in twenty-three it was found on subsequent examination and in thirty-one instances data recording metastasis were received from the attending physician or from relatives. Visceral metastasis occurred in fifty-six cases. There was involvement of the lungs in thirty, of the liver in thirteen, of the brain in five, of the spinal cord in two, of the spleen in one case, of the portal vein in one, of the heart in one, and of the pleura in three cases. Bony metastasis occurred in eleven cases, the humerus was involved in three, the sternum in one case, the femur in one, the ilium in one, the spinal column in two cases, the acetabulum in one case, the radius in one, and the ribs in one. Lymphatic involvement occurred in seventeen cases, the renal or adjacent nodes were affected in five, the retroperitoneal nodes in five, the aortic nodes in two, the mediastinal nodes in two, the axillary nodes in one case, the supraclavicular nodes in one, and the epitrochlear nodes in one. In fourteen cases surrounding structures were involved by direct extension: the suprarenal gland was involved in two, the ureter in two, the diaphragm in one case, and the peritoneum in three cases, a separate tumor overlay the spinal column in one case, there was intra-abdominal extension in three cases, and extension to the sigmoid in two. Distant metastasis was noted in thirteen of these fourteen cases whereas a definite recurrence occurred in two cases.

*Lungs*—Pulmonary metastasis was definite in twenty-four of thirty cases in which there was a subsequent history of pulmonary involvement or in which necropsy was performed. In this group there were eight deaths in the hospital. Necropsy was performed in eight cases, pulmonary metastasis was noted in both lungs in seven cases and in one lung in one case. Preoperative roentgenograms failed to demonstrate any evidence of metastasis in the eight cases in which necropsy revealed that the lungs were involved. In the six cases in which pulmonary



metastasis was present, the patients died within a year, the average length of life was 67 months. In the remaining ten cases, the patients lived from 15 to 75 years, the average length of their postoperative life was six years. In all 186 preoperative roentgenologic examinations of the thorax were made. One hundred and forty-seven (79.03 per cent) were reported as negative. In forty cases (21.50 per cent) there was notation of some condition in the chest other than metastasis.

Bumpus<sup>11</sup> recently reported a case in which there was apparent disappearance of pulmonary metastasis. The patient was a man, aged 59 years, on whom nephrectomy had been performed, Jan. 23, 1924. The tumor had destroyed half of the renal substance. A preoperative roentgenogram of the chest was reported as negative for metastasis. In January, 1925, the patient experienced sharp pain across the chest, associated with bloody sputum. During the next five months, he again noticed bloody sputum on five occasions. He gave an additional history of three attacks of transitory hemiplegia followed by dragging of the left foot. A roentgenogram of the chest, April 6, 1925, disclosed multiple metastatic areas in both lungs. In September, 1925, roentgenograms of the chest were reported as negative for metastasis, and the patient was in splendid health. In April, 1928, more than four years after nephrectomy, roentgenograms of the lungs were negative for metastasis. At the present time, more than five years following nephrectomy, the patient is apparently well.

*Nervous System*—In five cases in which nephrectomy was performed, symptoms subsequently developed, suggesting a tumor of the brain. In two of these cases, the patients returned for reexamination. In one of the cases the carcinoma of the kidney was reported as fixed at the time of operation and was diagnosed as adenocarcinoma. Five years later, because of recurrence of hematuria, the remaining ureter was removed and microscopic examination disclosed adenocarcinoma. Four months following this, symptoms developed suggestive of tumor of the brain. Exploration of the brain revealed a lesion that on microscopic examination was reported as hypernephroma. In the other case the growth at the time of nephrectomy had involved the renal vessels. Death occurred after three years. Symptoms developed before death suggesting a definite lesion of the brain stem. The home physician attributed the death of another patient of the five to metastasis to the brain. At the time of nephrectomy four years previously the renal lesion had appeared to be encapsulated and had been diagnosed as alveolar carcinoma. In two of the five cases symptoms developed later which were suggestive of involvement of the spinal cord. In one of these, an

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11 Bumpus, H. C., Jr. The Apparent Disappearance of Pulmonary Metastasis in a Case of Hypernephroma Following Nephrectomy, *J. Urol.* **20** 185, 1928.

operative note was made that all tumor tissue had not been removed. The patient lived ten months. Symptoms and data suggestive of tumor of the brain were present in two other cases in which operation or necropsy was not performed.

In three additional cases, not included in the five mentioned, observed at the clinic the symptoms were referable to the brain, and a diagnosis of tumor of the brain was made. Necropsy in two of these cases disclosed carcinoma of the kidney with definite metastasis to the brain. In the third case, carcinoma of the kidney was found at necropsy. Although an examination of the brain was not made in this case, the cerebral symptoms were attributed clinically to metastasis. As many of these patients have associated infection and are in the age when arteriosclerosis appears, it is often difficult to state whether or not a certain syndrome is best explained on the basis of inflammation, cerebral arteriosclerosis or metastasis.

#### ROENTGEN RAY AND RADIUM IN RELATION TO POSTOPERATIVE LENGTH OF LIFE

In addition to nephrectomy, treatment with roentgen rays was instituted in seventy-eight cases. Death occurred in fifty-one of these, after an average postoperative life of 24.37 months. In twenty-seven of the cases in which treatment with roentgen rays was given, the patients are living. The average postoperative length of life thus far has been 46.03 months. Roentgen rays and radium were used in twelve cases, death occurred in all after an average postoperative life of 35.09 months. Radium was used in nine cases, and death occurred in eight of these. One patient died while in the hospital, and seven died subsequently after having lived an average postoperative life of 10.57 months. One patient has been living for ninety-six months.

One hundred and eighty-four patients did not receive treatment with roentgen rays or radium following nephrectomy. Of these 184 patients, 121 are dead, twenty-nine died in the hospital and the remaining ninety-two died subsequently after having lived an average postoperative life of 30.61 months. The patients in sixty-three of the 184 cases in which roentgen rays or radium were not used in addition to nephrectomy are living. The average postoperative length of life, thus far, is 95.12 months.

It will be noted that when roentgen rays or radium were not used, the postoperative life of the patients still living is much longer than was the postoperative length of life in those cases in which treatment by roentgen rays and radium was used. The average postoperative life of patients who are still living and who did not receive treatment by roentgen rays or radium was 95.12 months, as compared with an average postoperative life of 46.03 months for those patients who are living and who received

treatment by roentgen rays alone. The patients who died following nephrectomy and who did not receive treatment by either roentgen rays or radium, postoperatively, lived an average postoperative length of time of 30.61 months, whereas the twelve patients who received treatment by radium and roentgen rays lived an average postoperative length of time of 35.09 months. It must be remembered, however, that the cases in which treatment by roentgen rays and radium was given were for the most part those cases in which all the tumor tissue had not been removed, in which the veins were involved or in which, for some reason, the prognosis was poor. Further, the radiotherapy was not always used



Fig 9—Bilateral papillary carcinoma. The patient was a man, aged 65 years, who had had hematuria intermittently for ten months. Five months previous to admission to the clinic he had undergone cystostomy elsewhere and probably a tumor had been removed from the bladder. Death was due to renal insufficiency on the fourth day following nephrectomy.

under supervision of physicians at the clinic, and we are not certain of the manner in which it was used.

#### BILATERAL HYPERNEPHROMA, HYPERNEPHROMA WITH POLYCYSTIC DISEASE AND HYPERNEPHROMA IN AN ECTOPIC KIDNEY

In one case in which death occurred following nephrectomy for adenocarcinoma, necropsy revealed a hypernephroma, 3.5 by 3 by 1.5 cm, in the remaining kidney (fig 9). Hypernephroma occurred in one case with bilateral polycystic kidneys. At necropsy the polycystic nature of the remaining kidney was verified. In another case in which poly-

cystic disease was suspected, but in which exploration alone seemed advisable, the patient lived for 4 5 years after operation. A later examination of a specimen removed from a region of metastasis in the aim revealed adenocarcinoma. In one case a huge adenocarcinoma occurred in an ectopic kidney. The mass had been present for six months, and the patient lived one year and nine months postoperatively.

#### CARCINOMA OF THE KIDNEY ASSOCIATED WITH LITHIASIS

In ten of the cases in which nephrectomy was performed in which the diagnosis was adenocarcinoma, renal lithiasis was associated, in eight the adenocarcinoma was found incidentally. In two cases the diagnosis of neoplasm had been made preoperatively. In four of the eight cases in which the malignant condition was an incidental observation, the patients have lived for eight years each. In one case the patient died in the hospital. In two other cases, there was an associated perinephric abscess, and the patients lived 2 5 years and 1 5 months, respectively. One patient was not traced.

#### RELATION OF NEPHRECTOMY TO POSTOPERATIVE LENGTH OF LIFE

In 250 of the 283 cases traced in which the patients were subjected to nephrectomy, the diagnosis was adenocarcinoma. One hundred and sixty-seven of these patients are dead, twenty-five died in the hospital, and 142 (63 11 per cent) died after having lived an average postoperative life of 29 67 months. In eighty-three cases (33 86 per cent) in which the patients are now living, the average duration of life has been 84 77 months. In thirty-three of the patients subjected to nephrectomy the diagnosis was alveolar carcinoma, twenty-five of these patients are dead. Five of these deaths occurred in the hospital, and twenty patients (71 42 per cent) died after living an average postoperative life of 16 86 months. In eight cases (28 57 per cent) in which the patients are now living, the average duration of life has been thirty-seven months. It may be noted that a higher percentage of patients in the group with alveolar carcinoma are dead, that is, 71 42 per cent, as compared with 63 11 per cent for the group with adenocarcinoma. The average postoperative length of life in the cases of alveolar carcinoma in which the patients have died was much shorter than the length of life in the corresponding group of patients with adenocarcinoma, 18 86 months as compared with 29 67 months.

The percentage of patients with alveolar carcinoma and with adenocarcinoma who are living is practically the same, however, the average length of life of patients with adenocarcinoma is greater than that of patients with alveolar carcinoma. Patients with adenocarcinoma have lived an average of 80 28 months, whereas those with alveolar carcinoma have lived for an average of thirty-seven months. The longest post-

operative life of any patient with alveolar carcinoma was six years and ten months, whereas twenty-six patients with adenocarcinoma have lived ten years or more

#### ANALYSIS OF THE DATA CONCERNING PATIENTS LIVING TEN YEARS OR MORE

In order to determine whether any singular factors might be noted, an analysis was made of the data in cases in which the patients are living ten years or more after operation. In this group of twenty-six patients there were eighteen men and eight women. The average age of the men was 49.77 years and of the women 48.12 years. The right side was involved in fifteen cases, and the left side in eleven. The average duration of symptoms before operation for the group was 36.92 months. The first symptom, in order of frequency, was pain in twelve cases, hematuria in nine and tumor in two, pain and hematuria occurred together in two cases and in one case the symptoms were not stated. A palpable tumor was demonstrated in eleven cases. The capsule was found broken at the time of nephrectomy in two cases, and definite perirenal extension was noted in six. In thirteen cases the gross specimens were recorded as large, in five, as medium, and in seven, as small, the size of one specimen was not stated.

These data show certain interesting comparisons in relation to the general group of patients subjected to nephrectomy. It may be noted that all the specimens were diagnosed as adenocarcinoma, the longest postoperative life in any case in which the diagnosis was alveolar carcinoma was six years and ten months. The average age of the patients was two years less than the average age for the entire group of patients who underwent nephrectomy. In this group in which the patients lived ten years or more, the right side was involved more often than the left side, whereas in the general group there were fewer tumors on the right than on the left side. Forty-two per cent of the patients had palpable tumors, as compared with 77 per cent in the entire group. The percentage of cases in which the renal capsule was broken through or in which perirenal involvement was noted at the time of nephrectomy is 30 for the group of patients who lived ten years, and 36 for the entire group. Of the gross specimens from the patients who lived ten years, thirteen (50 per cent) were recorded as large, whereas 161 gross specimens from the general group (57 per cent) were recorded as large. In six cases (23 per cent) the gross specimens from patients who lived ten years were recorded as medium. Seven (26 per cent) of the gross specimens from patients who lived ten years were recorded as small whereas thirty-six (13 per cent) of the specimens from the general group were recorded as small. In the group in which life endured for ten years or more, the percentage of patients presenting

large and moderate-sized tumors is less than for the general group in which nephrectomy was done, whereas the number of patients with small original growths is twice as large for the group in which the patients lived ten years as it is for the general group

#### PROGNOSIS

After a careful study of the data which have been set forth, one is impressed with the fact that the prognosis is dependent on many factors. The first factor that should be considered is the degree of cellular differentiation in the carcinoma. In none of the thirty-three cases in which nephrectomy was performed and in which the diagnosis from



Fig 10—Papillary adenocarcinoma. The lesion is well encapsulated, and is localized to the upper pole of the kidney. The patient was a man, 46 years of age, who had had intermittent hematuria for eighteen months before operation. The patient is living and well twenty-two and a half years after operation.

microscopic examination was alveolar carcinoma did the patient live more than six years and ten months. On the other hand, in twenty-six of the 250 cases in which the diagnosis was adenocarcinoma (hypernephroma) the patients have lived ten years or more. One of the patients has lived 22 1/2 years (fig 10). Symptoms are present for a shorter time, and the postoperative length of life is less among women than among men. Patients with small movable tumors may expect to live longer than those with extensively fixed tumors with involvement of perineal tissue. The hemoglobin at the time of operation bears a marked relationship to the rate of mortality. A percentage of hemo-

globulin of more than 70 offers a good prognosis. Metastasis occurs early and easily escapes detection, as is well demonstrated in seven cases with pulmonary metastasis in which preoperative roentgenograms of the thorax were reported negative, and necropsy shortly after operation showed definite metastasis.

Infection has a bearing on prognosis. It may be associated with obstruction to urinary drainage from blood clots, with obstruction from stones or with mechanical obstruction from extrarenal pressure. Another factor is the toxemia produced by the infection and by the absorption of degenerating tumor tissue.

The immediate mortality rate for nephrectomy was 9.61 per cent, 106 patients (51.45 per cent) have lived three years or more (fig. 11),

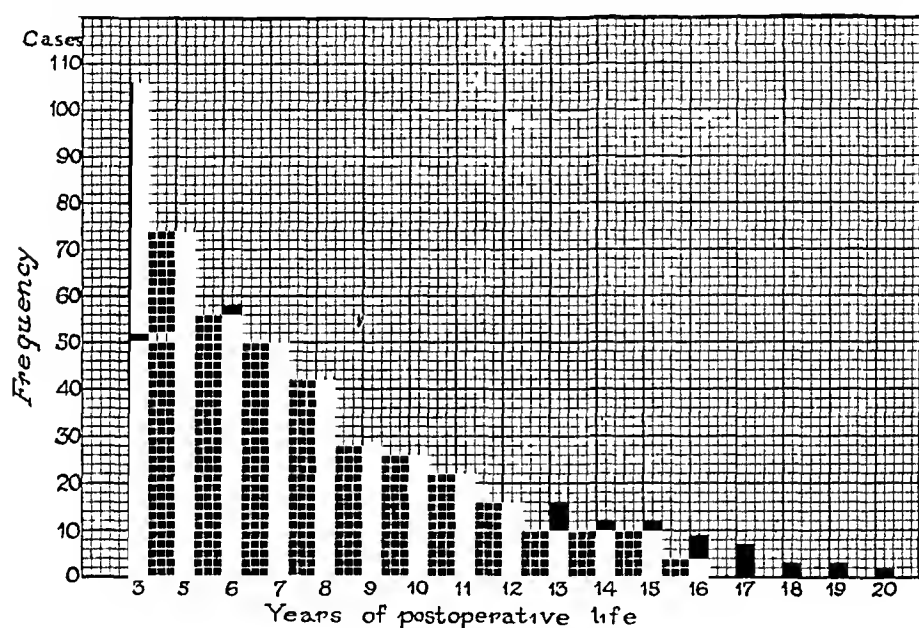


Fig. 11—Years of postoperative life of 106 patients with carcinoma of the kidney who lived three years or more.

seventy-four patients (35.92 per cent) lived five years or more, twenty-six patients (12.62 per cent) lived ten years or more. One patient, already mentioned in another connection, has lived more than 22.5 years.

#### SUMMARY

An analysis was made of 367 cases in which operation was advised for carcinoma of the kidney. Of this number, 330 have been traced. We wish to call attention to the fact that this paper includes cases in which operation was performed up to Jan. 1, 1928. Although insufficient time has elapsed since the operations done in recent years to warrant our drawing definite conclusions concerning the postoperative course of the patients, we believe that the general average of preoperative and post-

operative data presents many features worthy of record. Sixty-eight and thirty-nine hundredths per cent of the patients in the entire group were men and 31.60 per cent were women. The average age of the entire group was 51.76 years. The tumor involved the right side in 46.04 per cent of the patients and the left side in 53.40 per cent. Hematuria, pain and tumor were observed as the three cardinal features. Hematuria occurred as the first symptom in 43.86 per cent of the cases, pain in 37.32 per cent and tumor in 13.62 per cent. Of the 283 patients subjected to nephrectomy, who were traced, 192 are dead, having lived an average postoperative life of 23.26 months. There were thirty deaths in the hospital. Ninety-one patients are living, having lived thus far an average postoperative life of 60.88 months. Of forty-seven patients subjected to exploration alone, forty-five are dead, having lived an average postoperative life of 18.78 months. Two are living, one having lived thus far for an average postoperative life of 18.78 months. Metastasis occurred in seventy cases. Recurrence was reported in fifty-one cases. In the cases of involvement of the renal vein, the immediate mortality was not appreciably different from that observed in cases without involvement of the renal vein. However, the number of patients who died postoperatively is much higher among those with involvement of the renal vein.

Surgical approach through a posterior incision and removal of the upper portion of the ureter are significant factors in nephrectomy for carcinoma of the kidney.

The value of roentgen rays, radium or both as additional aids to surgery is difficult to estimate, since they are used only in those cases in which the prognosis is poor, namely, in cases in which there was extensive involvement of perirenal tissue and in which it was felt that all the tumor tissue was not removed. Treatment by roentgen ray in some of these cases was not always used under supervision of physicians of the clinic.

#### CONCLUSION

Carcinomas of the renal cortex are extremely malignant and are often well advanced before producing symptoms. Alveolar carcinomas, or those showing less cellular differentiation, are the most highly malignant, whereas adenocarcinomas (or papillary adenocarcinomas) are less malignant, as judged from their clinical course. Better end-results are dependent on earlier medical consultation by the patient after the onset of the initial symptom or sign. The end-results, as exemplified in the 106 cases in which the patients lived from three to 22.5 years, we believe justify nephrectomy for renal carcinoma.



# EOSINOPHILIC HYPERLEUKOCYTOSIS IN HODGKIN'S DISEASE WITH FAMILIAL EOSIN- OPHILIC DIATHESIS

REPORT OF A CASE AND REVIEW OF THE LITERATURE \*

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Moderate leukocytosis and slight eosinophilia have long been regarded as common components of the clinical picture of Hodgkin's disease. In few cases of authentic Hodgkin's disease, however, has there been recorded an excessive increase in eosinophilic cells of such magnitude as to warrant the designation "eosinophilic hyperleukocytosis." Such hyperleukocytosis, with absolute eosinophilia, has also been mentioned in association with various other unrelated diseases and has been described independently as an unclassified clinical syndrome. The following case is reported because, as a case of Hodgkin's disease, it is unique, both in the height of the leukocyte count and in the percentage and absolute number of mature eosinophils, and also, because it offers a possible explanation for this most unusual response of the bone-marrow.

## REPORT OF CASE

*History*—E. H., a woman, aged 35, was admitted on Sept. 14, 1928, to the University Hospital, service of Dr. Alfred Stengel, with enlarged nodes in the neck, cachexia, and irregular fever. Her illness dated back to 1918, when, following an upper respiratory infection, a transient swelling of the glands of the right side of the neck was first noticed. This swelling apparently disappeared and recurred at intervals. In 1921, another group of glands at the base of the neck became enlarged. Free use of iodine for several months was without effect. There was no fever and only slight loss of vitality. The weight, at that time, was 125 pounds (56.7 Kg.). The condition remained unchanged, except for some variation in the size of these nodes, until August, 1925, when quite suddenly there appeared a marked swelling of all the cervical glands on the right side. This condition persisted unchanged. In May, 1926, a tonsillectomy was performed. Microscopic study of the tonsils showed only "chronic inflammation." In the spring of 1927, two nodules appeared in the left popliteal space and shortly thereafter tender masses in both inguinal regions. Treatment with ultraviolet rays was ineffectual. During the fall of 1927, the patient was given tremendous doses of mercury and arsenic, by mouth. The reasons for this particular medication could not be elicited. Following this, the patient suffered a severe dermatitis (arsenical?), lasting several weeks. Coincidentally, the glandular enlargements entirely disappeared, only to recur to their previous size within a few weeks.

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\* From the Medical Division, Hospital of the University of Pennsylvania.

Weakness and loss of weight then became evident. A biopsy on a cervical gland in February, 1928, was reported to have shown only a chronic inflammatory process. Subsequently, all the symptoms of anemia, afternoon fever, severe sweats, diarrhea, and loss of strength and weight developed in rapid succession. The glands increased slightly in size, the lumps were noted in the right breast and in the abdomen. The past history and family history will be considered later.

*Physical Examination*—Significant data only are presented. The temperature was 102 F, the pulse rate, 100, respirations, 22, blood pressure, 108 systolic and 48 diastolic. The weight was 85 pounds (38.6 Kg). The patient was extremely

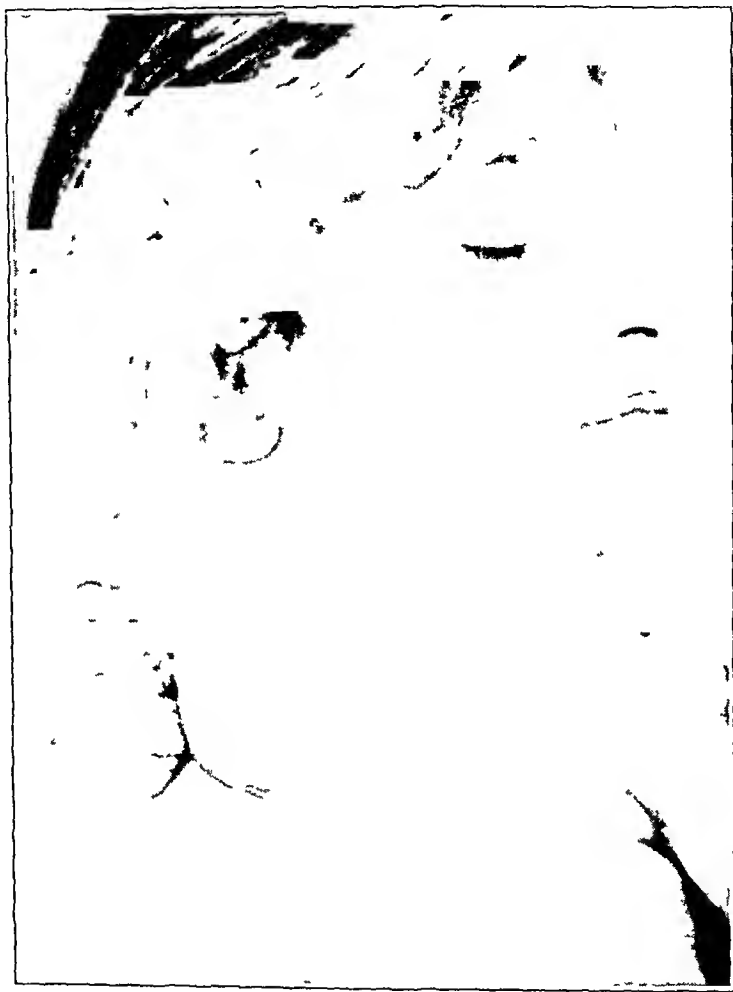


Fig 1—Patient E. H. The massive enlargement of the cervical lymph nodes of the right side of the neck should be noted.

emaciated, with a sallow, shiny, yellowish-tinted skin, and was obviously anemic and asthenic. The most striking feature was the glandular enlargement, as illustrated in figure 1.

The glands were quite firm, painless, discrete and freely movable beneath the skin. All of the cervical glands were enlarged, especially those on the right side of the neck. A few glands were found in both axillae, in the inguinal and femoral regions, in both breasts, and retroperitoneally. On the right side, the inguinal and femoral glands were extremely tender and soft.

The conjunctivae and mucous membranes were pale. Ophthalmoscopic examination revealed punctate retinal hemorrhages in both fundi. The heart was not enlarged. A loud blowing systolic murmur was audible everywhere over the precordium. The pulses were slapping, soft and easily compressible. The edge of the liver, which was palpable 3 cm below the right costal margin, was firm, rounded and smooth. The tip of the spleen was easily palpable 2 cm below the left costal margin.

*Course*—During the three months in the ward, the patient became steadily and progressively weaker. An irregular temperature varied from a subnormal level up to 103 F, and only subsided as a terminal event. Chills and severe sweats were not infrequent. Repeated transfusions maintained the red blood

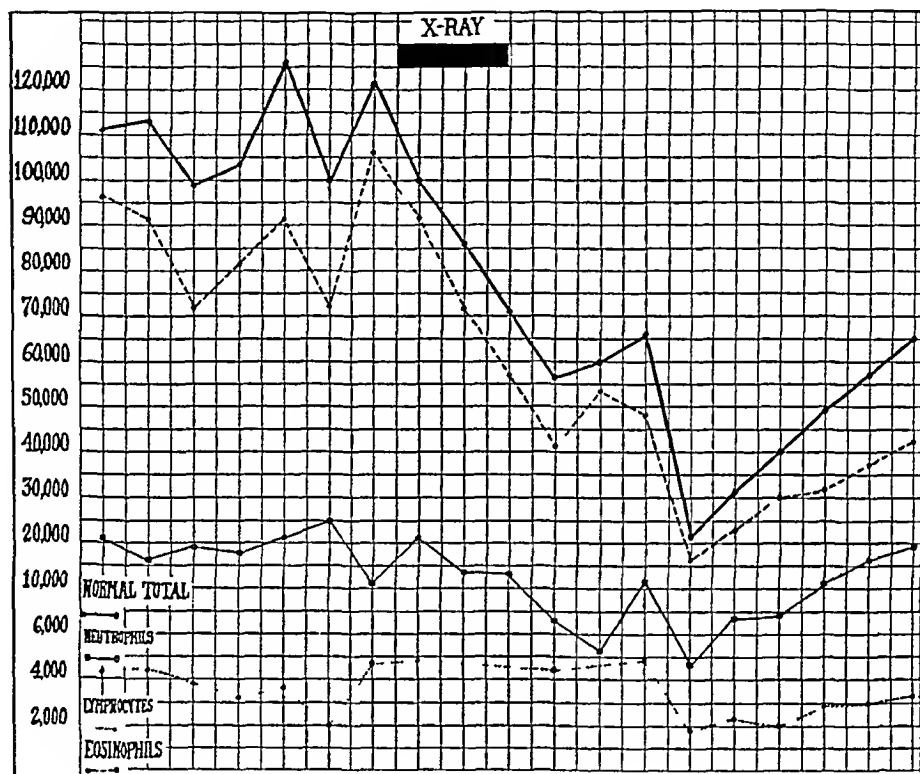


Fig 2—Graphic representation of the differential leukocyte counts in absolute numbers, taken at four day intervals, showing the effect of roentgen treatments

corpuscles at a safe level without improvement. A course of roentgen treatments was given over the long bones, abdomen and neck glands, and was finally discontinued because of vomiting and weakness. The effectiveness in reducing the size of the glands and the total leukocyte count were striking, as shown in figure 2. The retroperitoneal glands disappeared, the cervical glands became smaller, and the liver and spleen were perceptibly reduced in size. In spite of these encouraging results, the retrograde course continued, the liver suddenly became tremendously swollen, the heart action became weaker, and moist râles appeared at the bases of both lungs. Following several convulsions, the patient became comatose, the lungs filled with râles, and death ensued on Dec 27, 1928, as a result of cardiac collapse. The apparent duration of the disease, as estimated from the history of glandular swelling, was seven years.

*Laboratory Data*—The urine showed only a trace of albumin, a few white cells and hyaline casts. The Wassermann reaction of the blood was repeatedly negative. Blood chemistry studies were all within normal limits. Roentgen examination of the chest revealed no definite mediastinal involvement. There was a low free acidity of the gastric contents. The basal metabolic rate was +3 per cent. Skin sensitivity tests for the various foods, pollens and animal dander allergens and for arsenic were all negative. Because of the condition found on study of the blood, careful and repeated examinations of the stools were made, but no parasites or ova were seen.

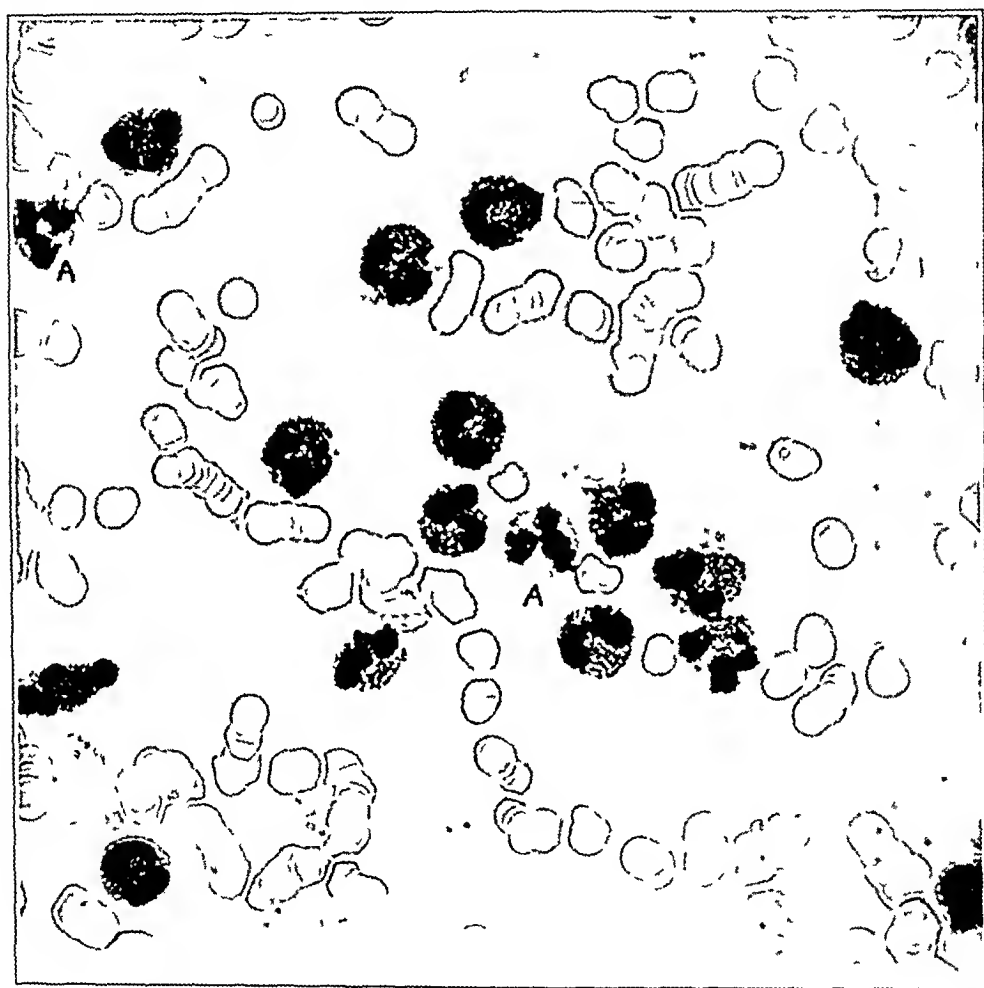


Fig 3—Blood film (Wright stain). Typical field, showing mature polymorphonuclear eosinophils and two polymorphonuclear neutrophils (A).

*Cytologic Study of the Blood*—The studies were made by Dr. Thomas Fitz-Hugh, Jr., of the department of hematology of the Hospital of the University of Pennsylvania. The observations of greatest interest in this case were the hyperleukocytosis and the persistent, high eosinophilia. Figure 2 shows an average total leukocyte count of more than 100,000 before roentgen treatments were instituted, and an analysis of the differential count reveals a percentage of eosinophils varying from 72 to 90. The polymorphonuclear neutrophils averaged 18 per cent and the lymphocytes, 4 per cent.

After the roentgen treatments, there was a progressive decrease in leukocytes to 20,000, with a gradual rise again after it was discontinued. In spite of this

precipitous fall in the leukocyte count, the differential count remained unchanged. By a comparison of the total number of each type of cell, it is apparent that the eosinophils account for the hyperleukocytosis, whereas the neutrophils, lymphocytes and large mononuclears are only slightly increased in total number above the proportion found in the majority of cases of Hodgkin's disease.

Practically all of the eosinophils were typical mature cells, with two or more lobulations of their nuclei, and large, highly refractile red granules of equal size



Fig 4—Cross-section of spleen, showing nodular masses and diffuse fibrosis

filling the cytoplasm. A few of the neutrophils were of the young type, classified as metamyelocytes, but no true myelocytes were seen in any of the examinations of the blood.

The red blood cell count was characteristic of a rather severe secondary anemia, averaging 2,800,000 cells, with a hemoglobin content of 45 per cent (Sahli). There was moderate anisocytosis and poikilocytosis. The platelet count remained around 130,000. In spite of frequent transfusions, there was only a slight improvement of the blood picture. The hemoglobin rose from 34 to 55 per cent, and the red blood cells from 2,400,000 to 3,000,000, with a decrease in anisocytosis.

*Autopsy*—Significant data only are given Autopsy was performed by Dr George Robson, of the department of pathology of the University of Pennsylvania

*Gross Examination* The spleen weighed 250 Gm and measured 11 by 10 by 5.5 cm The surface was firm and smooth, and mottled with dark red blotches Cut sections showed diffuse fibrosis Scattered through the organ were a number of grayish-white tumor masses, composed of soft, friable tissue definitely circumscribed and from 1 to 12 mm in diameter

The liver weighed 1,630 Gm and measured 23 by 19 by 8.5 cm The consistency was normal The cut surface showed nutmeg mottling with pale yellow zones in the periphery of each lobule The suprarenals weighed 3.9 and 5.6 Gm Both were smaller than normal and showed marked lipid exhaustion

The architecture of the kidneys was grossly normal Engorged medullary rays formed a striking contrast with the pale, mottled cortex The abdominal lymph nodes were composed of chains of enlarged nodes along the iliac vessels extending up along the aorta and vertebrae where the nodes were larger and partially fused The lower portion of the aorta and the upper portions of the iliac vessels were embedded in rather firm tissue which, on cut surface, showed enlarged lymph nodes of somewhat indistinct outline, and surrounded by white bands of fibrous tissue Along the bodies of the lumbar vertebrae, especially on the right side and extending up to the diaphragm, there was a large grayish mass made up of fused lymph nodes After removal of parts of the lumbar vertebrae, there was seen an actual invasion of this tissue through the periosteum into the bodies of the vertebrae to a depth of from 4 to 6 mm The lumbar muscles, which were in contact with the paravertebral mass, were also involved The lymph nodes about the celiac axis and in the mesentery and omentum were all slightly enlarged and quite firm The superficial glands have been described

The femoral bone-marrow was a uniformly dull grayish red

*Microscopic Sections* Numerous sections of lymph glands taken from various parts of the body showed different stages and degrees of the same process In a slightly enlarged pinkish-gray mesenteric node the lymph cords were intact, but the sinuses were dilated and lined by swollen endothelial cells The sinuses contained many actively phagocytic large mononuclear cells, apparently derived from their endothelial lining by desquamation, together with rather numerous red cells and eosinophils The lymph cords were intact but showed a few large pale endothelioid cells, closely packed lymphocytes, a few plasma cells, and numerous eosinophils Occasional giant cells of the Reed type were seen This picture of the highly cellular stage of Hodgkin's disease, with complete loss of typical architecture, was presented by most of the glands Some, however, showed more advanced stages with dense fibrosis and small scattered cellular areas, composed of endothelioid cells and lymphocytes, but with relatively few eosinophils All intermediate states between the highly cellular and the densely fibrotic types were represented

Sections from the large grayish tumor-like paravertebral mass showed a uniformly cellular structure devoid of any of the architecture of a normal lymph node but resembling the cellular type of node already described These sections were especially rich in eosinophils and showed giant cells of the Reed type The adjoining muscle was diffusely invaded

A section from one of the lumbar vertebrae which was in contact with the paravertebral mass also showed invasion The bone was completely destroyed, except for a few spicules, and was replaced by a cellular tissue of identical structure

The capsule and trabeculae of the spleen were relatively normal. The red pulp was strikingly engorged with blood and the dilated sinusoids lined by swollen endothelial cells. Numerous eosinophils were seen in the sinusoids. The follicles were inconspicuous. The general pulp showed no evidence of Hodgkin's disease. The nodular lesions, noted in the gross description, proved to be fairly definitely circumscribed but nonencapsulated cellular lesions of a structure identical with that of a paravertebral mass. Small necrotic and hemorrhagic areas were also present.

Many of the central arterioles were remarkable in appearance, because of a proliferative endo-arteritis frequently associated with thrombosis. This had pro-

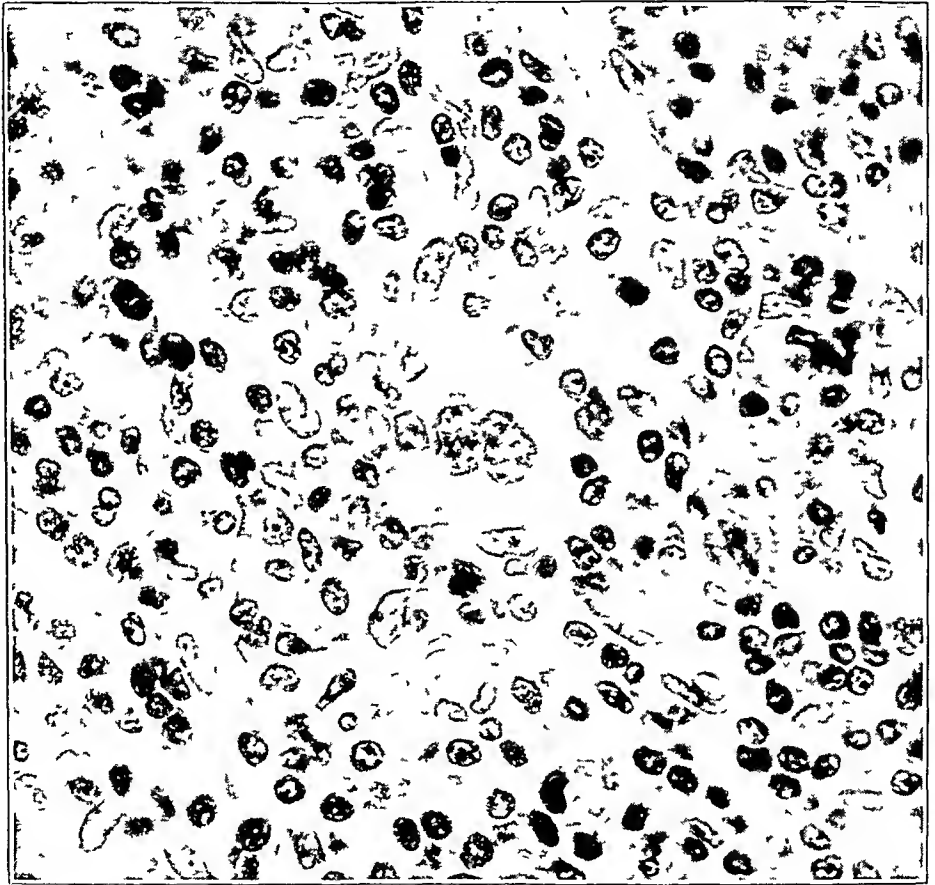


Fig 5—Lymph node (eosin-hematoxylin stain). A typical Dorothy Reed cell in the center of a field closely packed with lymphocytes, numerous large pale endothelioid cells, and eosinophils.

duced partial or complete occlusions in the affected vessels. This change was also present in the small arteries of the lymph nodes, kidney and liver, but was most pronounced in the spleen.

The architecture of the liver was normal. Passive congestion, parenchymatous degeneration, fatty infiltration and, in certain periportal areas, Hodgkin's tissue were seen.

There was cloudy swelling and passive congestion of the kidneys. In the outer zone of the cortex, in the interstitial tissue, were found small, dense collections of cells, similar to those found in the lymph nodes.

There was little adipose tissue in the bone-marrow. It was composed almost entirely of active hemopoietic tissue with a predominance of the cells of the granulocytic series. There were many eosinophilic myelocytes and phagocytes filled with deposits of hemosiderin. There was nothing to suggest Hodgkin's granuloma in the sections of bone-marrow.

A note by Dr. Herbert Fox, Director of the William Pepper Laboratory, Hospital of the University of Pennsylvania, stated: "A review of the sections reveals that the lesions are certainly consistent with the diagnosis of lymphogranuloma of the Hodgkin's type. There is one lymph node devoid of Hodgkin's histology,

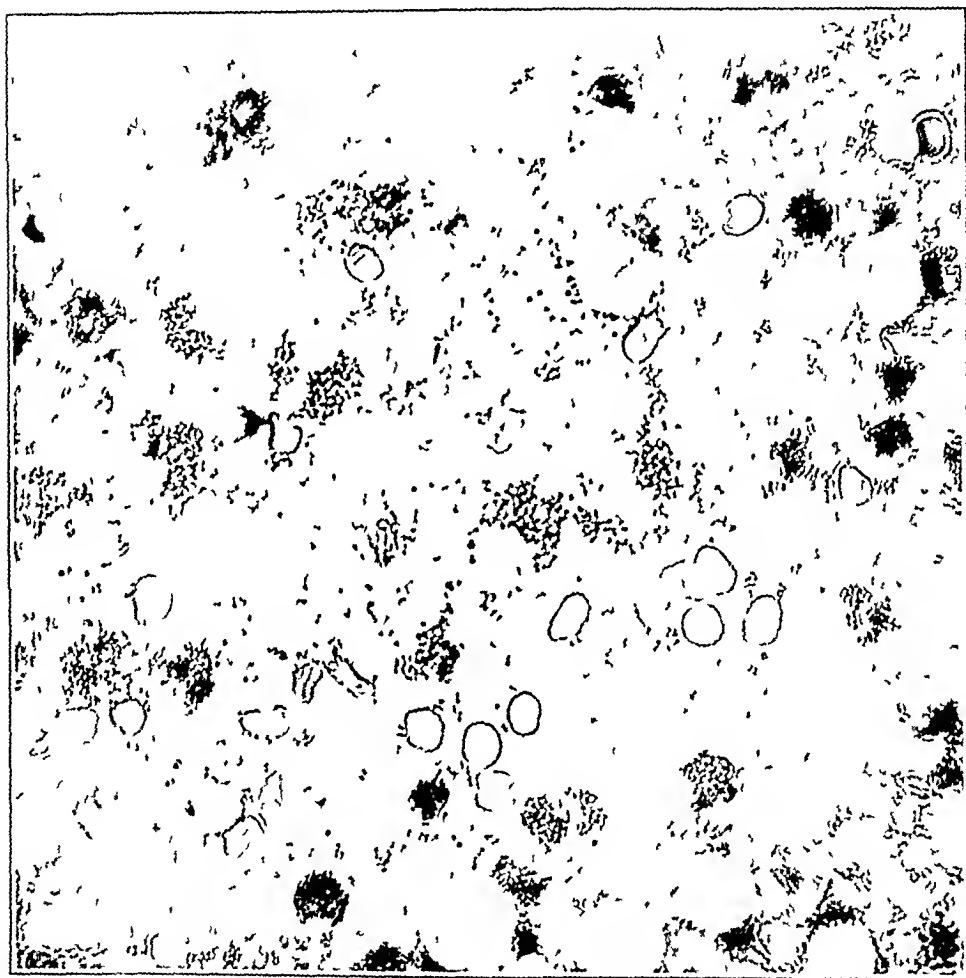


Fig 6—Smear of bone-marrow (Wright stain) illustrating engorgement with eosinophilic myelocytes. The scattered eosinophilic granules should be noted.

but it shows a very definite reticulo-endothelial hyperplasia, possibly a part of this process, possibly due to some other unexplained cause. There is a noteworthy change in the small blood vessels in all tissues. It is a tendency to productive meso- and endo-arteritis, with a tendency to thrombus formation.

"The most striking cellular character of all this tissue is eosinophilia. Where the lymphogranulomatous tissue is most cellular and least fibrous, and probably that part where it is the youngest, the eosinophilia is the richest. The bone marrow is hyperplastic in the myeloid series and eosinophils are the most numerous single cells."



## COMMENT

Clinically and histologically, this case was one of Hodgkin's disease, but it differed from Hodgkin's disease in its remarkable eosinophilic hyperleukocytosis. Only a few cases showing similar hematologic manifestations have been reported, but no authentic case of Hodgkin's disease showing such a marked eosinophilic diathesis was discovered in the literature. The problem of great interest is the interpretation of the blood picture in this case.

For a quarter of a century, since Goldman<sup>1</sup> first observed eosinophils in the lymph glands in a case of Hodgkin's disease, eosinophilia has been recognized as an integral part of the histologic picture in this condition. The presence of eosinophils was emphasized by Sternberg,<sup>2</sup> Reed,<sup>3</sup> Longcope<sup>4</sup> and others, although the diagnosis of Hodgkin's disease may be made with equal certainty in their absence. It seems, therefore, that eosinophilia in the majority of cases is a specific reaction of the bone-marrow in Hodgkin's disease.

Excessive eosinophilia, somewhat comparable to the author's case, has been recorded as occurring in supposedly true cases of Hodgkin's disease in few instances. The most marked cases that have been found reported in the medical literature are those listed in tables 1 and 2. Only two of these approximate the case reported here in the magnitude of the eosinophilia.

It is not impossible, in view of the similarity to the author's case, that some of these cases may belong to the Hodgkin's group. The diagnosis of eosinophilic leukemia has been suggested, but not accepted, as a clinical or pathologic entity. Admitting, for the sake of discussion, that eosinophilic leukemia exists, one could make out a case for this diagnosis in this patient (see Dr. Fox's note). Against this view, however, are the following observations: (1) the typical Dorothy Reed cells which were found in most of the biopsy and autopsy material examined in the patient, (2) the absence of myelocytic eosinophils in the blood stream, and (3) the fact that one of the large tumors of the lymph nodes failed to show the marked infiltration with eosinophils that characterized the other tumors, and

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1 Goldman, E. E. Beitrag zu der Lehre von dem malignen Lymphom, *Centralbl f allg Path u path Anat* **3** 665, 1892.

2 Sternberg, C. Ueber eine eigenartige unter dem Bilde der pseudoleukämie verlaufende Tuberculose des lymphatischen Apparates, *Ztschr f Heilk* **19** 21, 1898.

3 Reed, D. M. On the Pathological Changes in Hodgkin's Disease, with Especial Reference to Its Relation to Tuberculosis, *Johns Hopkins Hosp Rep* **10** 133, 1902.

4 Longcope, W. T. On the Pathological Histology of Hodgkin's Disease, with Report of a Series of Cases, *Bull Amer Clin Lab* **1** 4, 1903.

that one would postulate as necessary if this case were truly one of eosinophilic leukemia. It is assumed, therefore, that this case is acceptable as a proved case of Hodgkin's disease. The chief problem is to account for the remarkable eosinophilic diathesis.

TABLE 1—Cases from the Literature

Name	White Blood Cells	Percentage of Eosinophilia	Absolute Number of Eosinophils
Bunting Bull Johns Hospkins Hosp 27 173, 1914	20,000	68	13,600
Bunting	30,000	36	10,800
Barron Tr Scet Praet Med, 1923, p 309	55,000	44	24,200
Bonanno Pollelmico J <sup>3</sup> 1008, 1926	29,000	68	19,720
Dummel Wien Arch f Inn Med 13 283, 1926	16,000	26	4,160
Lincoln Boston M & S J 158 677, 1908	49,000	68	33,320
Pepper Bull Ayer Clin Lab 4 22, 1907	28,000	16	4,480
Weber and Bode Lancet 2 806, 1927	11,000	50	5,500

TABLE 2—Further Literary Review<sup>1</sup>

Author	Diagnosis	White Blood Cells	Percent age of Eosino-phils	Absolute Number of Eosino-phils	Percent-age of Myelo-cytes
Glanzmann Deutsches Arch f Klin Med 118 52, 1915	Lymphogranuloma tosa	183,000	33	60,390	2.6
Giffin Am J M Se 178 619, 1919	Eosinophilia with splenomegaly	211,000	90	189,900	0.2-0.7
Shapiro Tr New York Path Soc 19 73, 1919	Eosinophilic leukemia	236,000	79	186,400	0.65
McDonald and Shaw Brit M J 2 966, 1922	Eosinophilia with splenomegaly	138,000	80	110,400	0.7-4.7
Bass Am J M Se 170 416, 1923	Eosinophilia with splenomegaly	23,000	64	16,000	6
Stillman, M Rec S1 594, 1912	Myelogenous leukemia with eosinophilia	165,000	69	113,850	1.8
Alexander J Lab & Clin Med 9 803, 1924	Atypical myeloid leukemia	150,000	34	51,000	0.2
Schmidt-Weyland Med Klin 21 1767, 1923	Eosinophilic leukemia	90,000	67	60,300	
Sibley Brit J Dermat 27 52, 1915	Lymphadenoma	28,150	39	10,978	
Rheinbach Arch f Klin Chh 46 486, 1893	Lymphosarcoma	120,000	48	57,600	
Aubertin and Groux Presse med 29 314, 1921	Ayerza's syndrome	26,000	70	18,200	
Dunger Munchen med Wehn sehr	Carcinoma of colon	37,330	60	21,198	
Hay and Evans Quant J Med 1 167 (Jan) 1929	(1) Acute eosinophilic leukemia (2) Eosinophilic erythroleukemia	72,187 46,375	83 50	59,915 23,187	3.85

\* This table presents another small group of cases of lymphogranulomatous type with comparable hemocytologic manifestations. In this table are also included several unrelated cases with the same type of blood picture.

Weber and Bode advanced the theory that lymphogranulomatous involvement of the intestinal tract might have caused "a protective allergic reaction against absorbed foreign protein, or abnormal products of albuminous catabolic metabolism within the body." The

case of Schmidt-Weyland offered a similar explanation. Many cases, however, have been reported which showed extensive gastro-intestinal involvement by tumor without eosinophilia. McDonald and Shaw and Aubertin and Giroux suggested chronic anoxemia as a factor in the production of eosinophilia. Giffin stressed the chemotactic theory on the basis of toxemia with chronic infection. Lincoln, in his report of a case of Hodgkin's disease, hinted that the dyspnea in his patient might possibly have been true asthma and that the excessive eosinophilia could have been explained on an allergic basis.

In cases like the one here reported and those referred to, in which the tremendous eosinophilic hyperleukocytosis is so far out of proportion to the usual picture of primary pathologic change, it seems not unreasonable to believe that other factors may have been introduced. Therefore, all the usual causes of eosinophilia were investigated in relation to this patient, Mrs. E. H. Some interesting information was thus brought to light.

From the age of 2 to 7 years, the patient had frequent attacks of severe bronchial asthma. At the age of 7 the seizures stopped spontaneously and did not recur. In spite of the fact that a large number of skin tests showed no reaction, an allergic phenomenon must be considered as one of the probable factors in the explanation of the eosinophilia. This lead naturally suggested the importance of investigating the patient's relatives and her family history from the standpoint of allergy. The patient's paternal grandmother had severe asthmatic attacks for many years. Her mother had chronic eczema of the scalp. She presented herself for examination of the blood and was found to have from 5 to 6 per cent of eosinophils on three separate occasions. Two of the mother's brothers have had chronic eczema for years. No blood studies were obtained. The patient's brother has eczema and 6 per cent eosinophilia. Finally, the patient's son, who has had urticaria, showed from 7 to 8 per cent eosinophilia on three separate occasions.

This is an unusual example of allergic manifestation in four generations of a family, with abnormal blood eosinophilia in three generations. Only five case reports of so-called familial eosinophilia were found in the literature. In 1911, Klinkert<sup>5</sup> recorded the case of a family of six, the father and five children, with eosinophil counts of from 7 to 15 per cent, and with hypersensitivity to foods, urticaria, angioneurotic edema and asthma. Fanton<sup>6</sup> recently reported eosinophilia

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<sup>5</sup> Klinkert, D. Das Problem der konstitutionellen Eosinophilie, *Ztschr. f. klin. Med.* **89** 156, 1920.

<sup>6</sup> Fanton, E. So-Called Eosinophil Diathesis, *Clin. pediat.* **10** 295 (May) 1928.

in a father and daughter with no allergic history. Gauguier<sup>7</sup> observed a family in which the mother had 19 per cent eosinophils and three children, 10, 14 and 15 per cent, respectively, without any demonstrable cause. Cirio's<sup>8</sup> report was that of a healthy man with 66 per cent eosinophils, whose brother and children showed an eosinophilia of from 6 to 15 per cent. Lastly, the case of Bastai<sup>9</sup> was that of a girl, aged 17, whose mother and sister had an eosinophilia of 33 and 32 per cent, respectively, and who herself, had 27 per cent. During the course of an acute infection, the eosinophilia rose to 51 per cent.

An additional cause of eosinophilia in this patient may have been the dermatitis which followed massive arsenical therapy, even though the dermatitis had disappeared long before the patient came under observation. It is well known that dermatoses, in general, and arsenic poisoning, in particular, frequently produce eosinophilia.<sup>10</sup>

#### SUMMARY AND CONCLUSIONS

A case of Hodgkin's disease is presented, with report of the autopsy, which showed a tremendous eosinophilic hyperleukocytosis together with a marked increase of eosinophils in the bone marrow and the affected lymph nodes. The literature is reviewed. The exaggerated eosinophil response in this case is apparently due to (a) a well established familial allergic background, (b) a familial eosinophilic diathesis, (c) a personal allergic background, (d) the specific eosinophil stimulating effect of Hodgkin's disease itself and (e) the added effects of arsenic therapy.

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7 Bezançon and Moreau. L'eosinophilie dans les diatheses et les etats anaphylitiques, Reference to Gauguier's Family, *Ann de med* **2** 85, 1914.

8 Cirio, L. Sopra un caso di cosiddetta eosinofilia costituzionale, *Riforma med* **42** 219, 1926.

9 Bastai, P. Della eosinofilia costituzionale, *Haematologica*, 1923, part 1.

10 Latham, J. R. Exfoliative Dermatitis Due to Arsphenamine, *J. A. M. A.* **73** 15 (July 5) 1919. Moore, J. E., and Foley, F. E. B. Serious Reactions from Salvarsan and Diarsenol Brands of Arsphenamin, Unusual Blood Pictures, with Report of a Fatal Case, *Arch. Dermat. & Syph.* **1** 25 (Jan.) 1920.

## Book Reviews

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DIE BEDEUTUNG DES RETIKULOENDOTHELIALSYSTEMS FÜR DAS STREPTOKOKKEN-SEPSISPROBLEM By PROF DR N LOUROS and DR H E SCHEYER (der Staatlichen Frauenklinik Dresden) unter Mitwirkung von Dr A Schmechel and DR E GAESSLER Price, 14 marks Pp 96, with 13 illustrations and 4 colored plates Leipzig Georg Thieme, 1928

Stimulated by their interest in puerperal fever and septic abortion the authors undertook a systematic investigation of the general problems of septicemia caused by *Streptococcus*. This monograph summarizes the results of their experimental work on white mice in which several strains of streptococci of various degrees of virulence were employed. Attention was directed particularly to the reticulo-endothelial system in an effort to gain a better understanding of its role in combating such infections.

Certain morphologic and tinctorial changes in the cells of the reticulo-endothelial system are described, which the authors consider indicative of their functional capacity as a defense mechanism. In a search for agents which can stimulate the reticulo-endothelial system to heightened activity an enormous number of experiments were performed in which the microscopic observations were correlated with the ultimate outcome of the infection.

It was found that "blockade" with trypan blue and colloidal iron rendered mice more susceptible to infection. The parenteral administration of aqueous solutions of certain carbohydrates and of mineral salts and the feeding of vitamins was ineffective. On the other hand, various proteins and protein degradation products markedly increased the animal's resistance. Manganese chloride alone, of the heavy metal salts, had a similar though less striking effect. So did certain of a large series of lipoids and acid and alkaline buffer solutions, though still less marked. Roentgen irradiation in proper doses also rendered mice somewhat less susceptible. Various combinations of these methods of treatment were tried with the hope that a summation of beneficial effects might result, but they were all unsuccessful.

Immunization with killed and living cultures in proper doses rendered mice resistant to lethal doses of organisms. No immunity followed the injection of small numbers of streptococci into subcutaneous ajar foci. In many instances mice could be immunized against infection with toxin-producing strains by previous treatment with filtrates of old cultures, but the immunity was strictly strain specific. Vaccination with nontoxin-producing strains failed to raise the resistance to inoculation with toxin-producing strains. Antitoxic and antibacterial horse serums prepared by various commercial firms failed to protect, and in fact, one such serum seemed to increase the susceptibility of recipient animals to infection with the homologous strain.

The authors have performed an enormous number of experiments in a systematic fashion and they might have presented their results in a somewhat more convincing form. The number of protocols, for instance, is negligible. It is surprising that no cognizance is taken of the recent work of certain American investigators, particularly that of Swift and his co-workers, which is pertinent to some of their immunologic observations.

OLD AGE By ALDRED SCOTT WARTHIN, Professor of Pathology at the University of Michigan Price, \$3 New York Paul B Hoeber, Inc, 1929

The author describes the curve of life as made up of three periods: an ascending portion corresponding to the period of growth, a plateau of from 15 to 20 years representing maturity, and finally, a descending curve corresponding to retrogression and terminating in senescence. The biologic purpose of life is reproduction, "a potential immortality of its kind." Senescence begins at 60 with evidence of body

changes, but frequently without deterioration of the mental faculties. The only escape from senility is death from disease. Rejuvenescence is impossible. The increase in the span of life only increases the number of persons who reach this undesirable state. With this gloomy aspect, the reader looks forward with anticipation to the last chapter which deals with old age, the miseries and the methods of making the most of an undesirable condition. To those who reach this period with retained mental faculties added to the ripe experience of years, there may be much happiness, especially if the victim has been able to acquire hobbies which keep the mind young. In the author's description of senility, nothing gruesome has been omitted.

In this book, the author has given one the unvarnished truth. The person approaching three score, who reads this last chapter before retiring, is not apt to have pleasant dreams. After all, the author is a pathologist and not a practicing physician. His impressions of old age are obtained largely from the morgue. The physician, however, who is familiar with the family life, realizes that old age is not so gruesome. A picture of this period, with loving children, friends and grandchildren, is attractive and often inspiring.

LA FISIOPATOLOGIA CLINICA E SPERIMENTALE DELLA LIPEMIA. By MICHELE BUFANO. Paper. Pp 300. Milan. Soc An Istituto Editoriale Scientifico.

This is an excellent review of a difficult subject. The work is paper bound and of 300 pages without illustrations. It is the best monograph on the fats in many years, and should be made available to American readers.

The fatty acids, cholesterol, lecithin and all the lipoids are included in the studies, and the material is excellently coordinated so that the best possible insight is given into the little known field of the lipoids. The first few chapters cover the chemistry of these bodies in detail, and the various quantitative methods recently devised for their estimation. There follow chapters on the changes in the blood fat and various lipoids under physiologic conditions, such as starvation, exercise, feeding, etc. A serious attempt is then made to draw deductions from these data as to the metabolism of these substances and their physiologic significance. While exception might be taken to many points here brought up, it is probably the best that can be done in the present confused state of the problem.

The rest of the monograph is divided into a series of chapters on the fats and lipoids in various pathologic conditions in which they are known to be disturbed. The search through the world's literature has been thorough, and there is often added significant experimental work by the author. The diseases thus studied and reviewed include among many, diabetes, blood dyscrasias, nephropathies, neoplasms and infections.

WILLIAM HARVEY. By ARCHIBALD MALLOCK. Price, \$1.50. Pp 103, with 18 illustrations. New York. Paul B Hoeber, Inc., 1929.

This small volume of 100 pages is presented as a sketch of the life of William Harvey. In an age when the demand for condensation and selection is insistent and full biographies are not apt to be generally read, particularly by medical students and practitioners, a volume of this character meets an actual need. While Harvey and his work are, of course, inseparable, the author deals not so much with the evolution of his scientific achievements as with the sort of man Harvey was. His early training, contemporary influences and historical setting are delightfully depicted. One sees the master going about his daily work absorbed in his thoughts on the physiology of the circulation and exhibiting certain amusing idiosyncrasies in behavior, but by no means insensitive to the movement of life about him. One gathers the impression that while he was conscious of the importance of his own contribution to medicine, he was possessed of the dignified modesty characterizing all the truly great spirits of the past.

The book is well illustrated and contains an extensive bibliography. It constitutes a valuable addition to the series of pocket biographies put out by the same publishers.

L'UREMIE CONVULSIVE Par le DOCTEUR HENRI THIERS, Interne des Hopitaux, Lyon Paper Pp 226 Imprimerie Bosc Freres et Riou, 1928

This book can be recommended to those who desire to read in good French a review of past and present opinions of French observers of uremia in general and the occurrence of uremic convulsions in particular Little mention is made of contributions not written in French Twelve cases observed by the author are related In his conclusions he states that convulsions may occur in any renal condition capable of producing uremia, but comments on their rarity in tuberculous and "surgical" diseases of the kidney Convulsions often occur after diminution of edema and are more frequent in persons with history of previous nervous ailments or of syphilis Stress is laid on the diagnostic importance of lumbar puncture as meningeal and cerebral diseases often are associated with or may simulate uremia Thiers states that the cause of convulsive uremia remains entirely unknown but attaches some importance to Blum's ideas of "uremic cerebral dysmineralization" He is puzzled, however, by the constancy of chloride retention in all kinds of uremia and by the rarity of convulsions

GALLENSEKRETION UND GALLENENTLEERUNG By DR D ADLERSBERG Price, 5 marks Pp 76, with 4 illustrations and 12 tables Leipzig Franz Deuticke, 1929

The author publishes in monographic form his clinical and experimental observations on the secretion and flow of bile, citing the literature as it bears on the subject under discussion He finds that pituitary in man has, at the same time, a cholekinetic and an anticholeretic action, and has considerable diagnostic significance in disease of the biliary passages He records his studies on bile sediment after the administration of "decholin" and attaches diagnostic significance to his results He reviews his results following the use of various therapeutic agents on diseases of the biliary passages, citing numerous cases Every one interested in the study and diagnosis of disease of the biliary ducts should have a copy of this monograph at hand

PRACTICAL CLINICAL LABORATORY DIAGNOSIS By CHARLES C BASS and FOSTER M JONES Third edition Price, \$7 50 Pp 187 Baltimore Williams & Wilkins Company, 1929

The material covered by this book has been chosen rather arbitrarily, as has also been the case in the method selected for each test For instance, a method is given for determination of blood sugar, but none is included for any determination of blood protein Only one counting chamber is described and that is not to be found universally While fourteen pages are devoted to blood counting, no mention is made of the simple theory pertaining thereto The material which is presented is given clearly although verbosely Not a few of the many illustrations are valueless though technically good The book should serve best medical students with a limited premedical and preclinical training

## RATE OF EVACUATION OF VARIOUS FOODS FROM THE NORMAL STOMACH

A PRELIMINARY COMMUNICATION<sup>1</sup>

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Since the time of Beaumont it has been known that proteins pass out of the stomach more rapidly than fats, and that carbohydrates are evacuated still more quickly. As the hypotheses advanced in explanation of these differences appeared to be inadequate, it seemed to us advisable to do some further work on this subject, especially with reference to the question why fats are held in the stomach so much longer than carbohydrates. During the course of the investigation, the differences in behavior of substances having little or no food value excited and retained our interest.

Beaumont's observations on the time of evacuation of carbohydrates, proteins and fats, have been confirmed by many workers employing various methods. Penzoldt<sup>1</sup> passed stomach tubes in a number of men. Pavlov<sup>2</sup> and his pupils used dogs with duodenal and other kinds of fistulas. Cannon<sup>3</sup> made roentgen observations on cats, estimating the degree of gastric emptying from the length of the shadows in the intestine. Fermi<sup>4</sup> killed dogs at definite intervals after meals, and weighed the dried gastric residues. McClure, Reynolds and Schwartz<sup>5</sup> mixed barium sulphate with food, and observed the passage fluoroscopically in man. They found that all substances commence to leave the stomach as soon as ingested, but that the total evacuation of some materials was much slower than that of others. Hawk, Rehfuess and Bergeim<sup>6</sup> passed small tubes into the stomachs of human subjects, and

<sup>1</sup> Submitted for publication, May, 1929.

<sup>2</sup> From the Department of Medicine and the Department of Radiology of the University of Toronto.

1 Penzoldt, F. *Deutsches Arch f. klin. Med.* **51** 535, 1893.

2 Pavlov, I. P. *The Work of the Digestive Glands*, ed. 2, London, 1910.

3 Cannon, W. B. *Am. J. Physiol.* **20** 283, 1907.

4 Fermi, C. *Arch. f. Physiol.*, 1901, supp., p. 1.

5 McClure, C. W., Reynolds, L., and Schwartz, C. O. *On Behavior of Pyloric Sphincter in Normal Man*, *Arch. Int. Med.* **26** 410 (Oct.) 1920.

6 Hawk, P. B., Rehfuess, M. E., and Bergeim, O. *Am. J. M. Sc.* **171** 359, 1926.



removed small portions of the meals at intervals. They found the average evacuation time for 100 Gm of beef to be three hours, puddings, two and one quarter hours, bacon, four and one half hours, etc.

Pavlov, and later Cannon, explained the differences in the rate of evacuation by the hypothesis of the acid control of the pylorus. This hypothesis was, in brief, that any acid in the antrum opened the pyloric sphincter, whereas the presence of any acid in the duodenum resulted in closure of the pylorus until such time as the duodenal contents had been neutralized. On leaving the stomach, carbohydrates are neutral and proteins are distinctly acid, whereas fats are broken up into fatty acids and glycerol on arrival in the duodenum. This hypothesis, therefore, fitted in with the known facts and seemed to explain satisfactorily the differences observed.

Support of the acid control hypothesis was found in the work of Lintwarew,<sup>7</sup> who placed fat in the duodenum and observed that gastric evacuation was thereby markedly slowed. It is of interest to note that Edelman<sup>8</sup> failed to find the same effect with petrolatum. Marbaix<sup>9</sup> found that the emptying of the stomach was delayed when he placed milk or egg yolk in the jejunum. Tonnis and Never<sup>10</sup> recently showed that any free acid, fatty or otherwise, when injected into the duodenum caused closure of the pylorus, whereas neutralized fatty acids had no such effect. Procaine hydrochloride abolished the reflex closure.

The following observations, however, raised doubts as to the truth of the acid control hypothesis. McClure, Reynolds and Schwartz<sup>5</sup> observed that neutralizing the duodenal contents had little effect on the rate of gastric evacuation, and further showed that the pylorus opened and chyme entered the duodenum "on the approach of each antral peristaltic wave." In Cannon's<sup>11</sup> own experiments the chyme left the stomach as peristaltic waves approached the pylorus, though not with every wave. Baird, Campbell and Hern<sup>12</sup> found that acid in the duodenum did not close the pylorus. Sick and Tedesco<sup>13</sup> placed acids and alkalis in the duodenum and observed no change in gastric or pyloric activity. Carlson and Litt,<sup>14</sup> employing an improved balloon method, found that any substance, acid, alkaline, or neutral, when placed

7 Lintwarew, S. J. *Biochem Central* **1** 96, 1903

8 Edelman, J. A., quoted by Babkin, B. P. *Die aussere Sekretion der Verdauungsdrusen*, ed 2, Berlin, 1928, p 824

9 Marbaix, O. *Cellule* **14** 251, 1898

10 Tonnis, W., and Never, H. E. *Arch f d ges Physiol* **207** 24, 1925

11 Cannon, W. B. *Am J Physiol* **1** 359, 1898

12 Baird, M. M., Campbell, J. M. H., and Hern, J. R. B. *Guy's Hosp Rep* **74** 23, 1924

13 Sick, K., and Tedesco, F. *Deutsches Arch f klin Med* **92** 416, 1908

14 Carlson, A. J., and Litt, S. *Visceral Nervous System. Reflex Control of Pylorus*, *Arch Int Med* **33** 281 (March) 1924

in the duodenum caused closure of the pylorus. Finally, Barsony and Hortobagyi<sup>15</sup> showed that strong acid in the duodenum inhibited gastric emptying, but not because of pyloric closure. The delay was due to depression of the peristaltic waves of the stomach.<sup>16</sup>

As it becomes evident that acid control is not the only factor, or even the principal influence, in determining the rate of the emptying of the stomach, more and more is attention being turned to the mechanical forces involved, and especially to gastric peristalsis. It therefore becomes of interest to consider the factors which are known to influence peristalsis and gastric evacuation, and the following is a partial list of these.

The physical state of the foodstuff is of considerable importance, as gruel leaves the stomach more rapidly than dry carbohydrates (Hedblom and Cannon<sup>17</sup>), and large lumps of meat are retained much longer than minced meat (London<sup>18</sup>). Posture and exercise have marked effects (Neilson and Lipsitz,<sup>19</sup> Dickson and Wilson<sup>20</sup>), changes in the carbon dioxide content of the blood have a great influence (Dickson and Wilson), also the rate of utilization of glycogen (Bulatao and Carlson<sup>21</sup>), emotions (Cannon,<sup>11</sup> Bennett and Venables,<sup>22</sup> Hughson<sup>23</sup>), fractures of bones (Alvarez<sup>24</sup>), colonic irritation (Hedblom and Cannon,<sup>16</sup> White<sup>25</sup>), smoking, drinking water with meals (Ivy<sup>26</sup>) and many drugs such as strychnine, atropine, caffeine and alcohol. It is highly probable that other influences will be found to affect both peristalsis and the rate of emptying, and it is possible that the increased fat in the blood after a fat meal (Neisser and Braeuning,<sup>27</sup> Bloor<sup>28</sup>) may be one of these.

15 Barsony, T., and Hortobagyi, B. *Arch f d ges Physiol* **210** 300, 1925

16 For a more extensive review of the work on this subject, see Alvarez. *The Mechanics of the Digestive Tract*, ed 2, 1928, p 175, also Babkin. *Die aussere Sekretion der Verdauungsdrusen*, ed 2, 1928, p 802

17 Hedblom, C. A., and Cannon, W. B. *Am J M Sc* **138** 504, 1909

18 London, E. S. *Experimentelle Physiologie und Pathologie der Verdauung*, Berlin, Urban & Schwarzenberg, 1925, p 52

19 Neilson, C. H., and Lipsitz, S. T. *The Effect of Various Procedures on the Passage of Liquids from the Stomach*, *J A M A* **64** 1052 (March 27) 1915

20 Dickson, W. H., and Wilson, M. J. *J Pharmacol & Exper Therap* **24** 33, 1924

21 Bulatao, E., and Carlson, A. J. *Am J Physiol* **69** 107, 1924

22 Bennett, T. I., and Venables, J. F. *Brit M J* **2** 662, 1920

23 Hughson, W. *Reflex Spasm of Pylorus and Its Relation to Diseases of Digestive Organs*, *Arch Surg* **11** 136 (July) 1925

24 Alvarez, W. C. *The Mechanics of the Digestive Tract*, ed 2, 1928, p 197

25 White, F. W. *Am J M Sc* **156** 184, 1918

26 Ivy, A. C. *Am J Physiol* **46** 420, 1918

27 Neisser, E., and Braeuning, H. *Ztschr f exper Path u Therap* **4** 747, 1907

28 Bloor, W. T. *J Biol Chem* **23** 317, 1915

## METHOD

In this investigation, roentgen observation of the human subject was adopted as the method which best met our requirements. All the experiments were performed on four young men who had no symptoms of gastro-intestinal or other disease, and whose stomachs had previously been found to be normal on fluoroscopic examination. All had fasted for at least four hours preceding the experiments. The subject was given a meal containing 40 Gm of barium sulphate made up to 240 cc, with the substance to be investigated. Fluoroscopic observations were made during the consumption of the meal, with the object of determining how soon the food commenced to leave the stomach. Subsequent observations were made at one and one-half, three and four and one-half hours after beginning the ingestion of the meal, and at each examination an estimate was made of the percentage of the barium remaining in the stomach. The results are expressed as the percentage of the meal which had been evacuated from the stomach.

In some instances the meals employed were patterned on those described by McClure, Reynolds and Schwartz.<sup>5</sup>

Standardization has been achieved in the amount of barium, the volume and temperature of the meal, the time of the day and the day of the week on which it was consumed, and the amount of exercise of the subject. If the subject had a "cold in the head," or otherwise did not feel well, the experiment was deferred. Nearly all the observations of the percentages in the stomach were made by one of us (A. C. S.), and all were checked by one of the others. We are therefore confident that any errors due to method have been reduced to a minimum. It is probable that no change has occurred in the motility of subject D's stomach during the four years that this investigation has been in progress, for a meal of thick oatmeal porridge consumed March 21, 1929, behaved in every respect almost exactly like a similar meal taken March 4, 1925.

The observations with respect to meals consumed by two or more subjects are summarized in table 1. A further series of experiments was performed on subject D, and all the observations on this person are shown in table 2.

## COMMENT

Any discussion of gastric emptying must of necessity bring up the question of the physical forces which are concerned in that emptying. Among these forces are gravity, the contraction of the stomach as a whole and gastric peristalsis. It is not our intention to discuss this question in this paper. It can be stated, however, that with one exception, in the experiments here recorded, no barium was ever seen to enter the duodenum except on the approach of a gastric peristaltic wave. The single exception was in the case of the meal containing 30 Gm of Witte's peptone. The first mouthful passed through the stomach, pylorus, duodenum and upper part of the jejunum in the course of a few seconds, then the shadow was halted in the region of the pyloric sphincter, and no further emptying occurred until five minutes later, when peristalsis had become established.

TABLE 1—Observations on Four Subjects with Six Different Meals\*

Subject	Thick Porridge 210 Gm			100 Gm Dates and Bread 10 Gm			110 Gm Ground Ice in Meat			120 Gm Fat Bacon 5 Egg Yolks			210 Gm 32 per Cent Cream			210 Gm 32 per Cent Cream + 0.5 Gm Hydrochloric Acid		
	Percentage Out in			Percentage Out in			Percentage Out in			Percentage Out in			Percentage Out in			Percentage Out in		
	First Leav- ing	1½ Hrs	3 Hrs	First Leav- ing	1½ Hrs	3 Hrs	First Leav- ing	1½ Hrs	3 Hrs	First Leav- ing	1½ Hrs	3 Hrs	First Leav- ing	1½ Hrs	3 Hrs	First Leav- ing	1½ Hrs	3 Hrs
A	1	85	100				3	50	75	15	20	30	2	?	10	2	10	30
B	2	70	100				1	70	60	31	10	50	2	10	50	1	30	40
C	3	95					12	70	100				2	50	65			
D	4	75	90				7	40	80	12	10	30	1	75	80	1	710	75

\* With each meal the first column shows the time in minutes after the commencement of ingestion that barium was first seen in the duodenum. The other three columns give the percentage of the meal which has left the stomach in one and one-half, three and four and one-half hours, respectively. Each meal totals 210 cc and contains 40 Gm of barium sulphate.

For our present purpose, therefore, we shall assume that gastric peristalsis is the principal force concerned in normal gastric evacuation.

The rôle of the pyloric sphincter in influencing normal gastric emptying is another question that we shall not discuss here. In all our

TABLE 2—*Observations on Subject D*

Meal	Minutes to Swal- low	First Leav- ing	Percentage Out in			Comment
			1½ Hrs	3 Hrs	4½ Hrs	
Thick porridge	3	4	75	90		
Thick porridge	2	4	75	95		
Thick (7½ hours after	3	5	65	85	100	
porridge/400 cc 32 per cent cream	2	6	75	80	85	
Thick porridge, plus 13 cc hydrochloric acid (38%)	3	5	60	90	100	
Very thick porridge, plus 13 cc hydrochloric acid (38%)	3	22	10	75	85	
Thick porridge, 200 Gm, washed bran, 24 Gm	4	38	35	60	70	
Bread, 40 Gm, dates, 100 Gm	3	3	60	95		
Meat 140 Gm, ground, lean, baked	5	7	40	80	90	
Codfish, boiled, 160 Gm	5	20	30	85	95	Contains no carbohydrates
Egg white, raw, 225 Gm	1	5	30	65	85	
Egg white, raw, 220 Gm	1	3	75	85	90	Put through sieve
Egg white, cooked, 190 Gm	5	41	65	95		
Gelatin, 15 Gm, white of egg (1)	2	5	60	90		
Witte's peptone, 30 Gm in water	1	½	90	95		
Witte's peptone, 70 Gm in water	1	10	30	60	85	Very viscid
Asparagin, 35 Gm, in water	1	1	75	100		
Cream 32%	1	1	75 ?	80	85	Severe cramps
Cream, 32%	1	1	25	40	70	Severe cramps
Cream plus tube	1	1	10 ?	60	95	Tube in duodenum continuous suction
Cream plus tube	1	1	25	75	100	Tube in duodenum, no suction
Cream plus 0.5 Gm hydrochloric acid	1	1	10 ?	75	85	Free acid, 0, total acid, 40
Cream plus 5 Gm NaHCO <sub>3</sub>	1	1	25	40	80	
Bacon, 120 Gm, plus 5 egg yolks	5	12	10	30	95	
Olive oil	1	1	25	50	60	Severe cramps
Liquid paraffin	1	2	80	100		No discomfort
Liquid paraffin, 195 cc, 32% cream, 45 cc	1	½	75	100		
Liquid paraffin, 150 cc, salt free butter, 90 Gm	1	½	60	80	90	Contains approx same amount of butter fat as 32% cream
Bran, washed, 37 Gm, wet	12	90+	0	20	35	Contains 3 per cent carbohydrate
Bran, washed, 30 Gm, wet	25	51	20	35	50	
Bran, washed, 25 Gm, wet	7	80	2	25	40	More finely divided than above
Bran, unwashed, 38 Gm, wet	12	32+	20	35	50	Contains 50 per cent carbohydrate
Agar, 15 Gm in water	5	19	40	65	85	
Cabbage, ground, thrice boiled	2	25	25	60	70	200 Gm wet weight contains no carbohydrate
Spinach, ground, thrice boiled	3	28	60	90	100	240 Gm wet weight contains no carbohydrate

\* The first column gives the time in minutes taken to swallow the meal. The second column shows the time after the commencement of ingestion that barium was first seen in the duodenum. The other three columns give the percentage of the meal which has left the stomach in one and one-half, three and four and one-half hours, respectively. Each meal totals 240 cc and contains 40 Gm of barium sulphate.

observations, however, except in the experiments with bran, every peristaltic wave of any considerable depth effected an expulsion of barium into the duodenum, provided that barium was in contact with the sphincter. Shallow waves at the commencement of the meal may

not cause emptying for one or two minutes, and toward the end of an experiment the remaining barium may be seen in a narrow band along the most dependent part of the greater curvature when the subject is standing and hence may not be evacuated even by deep peristaltic waves. Our impression is that the pyloric sphincter behaves as a part of the gastric musculature, being strongly contracted only on the arrival of a peristaltic wave, and that normally it has no independent influence on evacuation in the stomach.

The question of the effect of acid on gastric evacuation is too involved for adequate discussion here. The following points, however, seem worthy of note. For many years we have observed that, in patients with organic lesions or functional disturbances, meals consisting of buttermilk and barium sulphate have been associated with shallow peristalsis, pylorospasm, and retarded gastric evacuation, as compared with watery suspensions, or meals of barium and whole milk. The pylorospasm is usually temporary, seldom persisting for more than from five to ten minutes.

In two experiments on subject D, porridge meals were made strongly acid with hydrochloric acid. The results were inconclusive, after one meal shallow peristalsis and retarded evacuation were observed, while observations following the other were normal.

*Filling of the Stomach*—In order to understand the passage of a meal through the pyloric sphincter, it will be necessary to consider the manner in which the meal traverses the stomach in order to reach the sphincter. Meals of different consistency behave differently in this respect. A liquid meal such as cream, weak peptone solution or liquid paraffin at once forms a narrow streak along the whole length of the stomach from the cardia to the pyloric sphincter. As swallowing continues, the stomach widens. A meal of this type was commenced at 4 30 and finished at 4 30 40 (fig 1).

A more solid meal, however, at first forms a ball at the cardiac end of the stomach, and then this mass becomes pointed and slowly descends to the region of the pylorus. The meal of spinach for example behaved as shown in figure 2.

This meal was commenced at 3 30 and finished at 3 36 (compare Groedel<sup>29</sup>).

*The Initiation of Peristalsis*—Peristalsis of the stomach was visible, in the case of nearly all liquid meals, within one minute of the commencement of ingestion, and continued to be visible until only a small quantity of barium remained in the stomach. On the other hand, after a more solid meal, such as ground lean meat, codfish or cabbage, no peristaltic waves could be seen until the "head" of the meal had reached

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29 Groedel, F. M. *Die Magenbewegungen*, Hamburg, 1912.

the pyloric sphincter. Thus peristalsis commenced much earlier with liquid meals than with solid ones. The nature of the initial stimulus to peristalsis is a matter of considerable interest, but at present we can only speculate on this problem. It cannot be due to the presence of material in any part of the stomach, for in one experiment in which bran was used the meal filled the whole of the stomach, including the pyloric part, for at least forty-five minutes without a trace of peristalsis, and Rogers and Martin<sup>30</sup> have shown that peristaltic waves can occur when the stomach contains nothing but the normal gas bubble. It cannot be due to absorption from the stomach, for peristalsis commenced immediately after the ingestion of barium and liquid paraffin, which are not absorbed.

*The Depth of Peristaltic Waves*—With all fluids the waves were shallow for a minute or so, and then became deeper, later they became

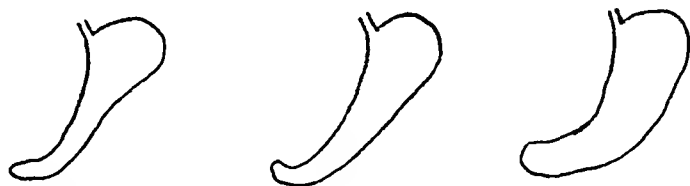


Fig 1—Appearance of stomach at 4 30 20, 4 30 40, and 4 31, respectively, following the ingestion of a liquid meal



Fig 2—Appearance of stomach at 3 36, 3 41, 3 46, 3 51 and 4 01, respectively, following the ingestion of a more solid meal

shallow again in the case of cream, olive oil and a mixture of liquid paraffin and butter, but remained deep with liquid paraffin alone, with weak peptone solution, and with asparagin (an amino-acid) and water. Thus the waves became shallow with fat meals, but remained deep in the case of meals which contained no fat. The interpretation of these observations will be considered a little later.

*The Initial Emptying of the Stomach*—The initial emptying depends, in the first instance, on the presence of meal material in the region of the pyloric sphincter, and this, as already shown, varies with the consistency of the meal. Thus the first evacuation is rapid for all liquids and slow for all solids. Within one or two minutes of the “head” of the liquid meal reaching the pyloric sphincter, some barium was seen

30 Rogers, F T, and Martin, C L. Am J Physiol 76 349, 1926

to enter the duodenum. The same was true for solid meals, with a few exceptions, the most important of which were meals containing bran. In one experiment in which bran was used the stomach was quiescent, without peristalsis, and with barium apparently in contact with the pyloric sphincter, for at least forty-five minutes. As soon as peristalsis became established, some of the bran entered the duodenum. Thus the presence of adequate peristalsis is a second requirement for normal gastric evacuation.

The influence of the consistency of the meal was shown in another experiment with bran. In this observation, peristalsis commenced as soon as the "head" of the meal reached the pyloric sphincter, following this, at intervals for over an hour we watched the peristaltic waves sweeping over the stomach, without the least fleck of barium entering the duodenum. Our impression during the observation was that emptying was hindered by friction of the bran with the mucous membrane of the stomach, rather than by obstruction from a closed pyloric sphincter. Subsequently barium left the stomach regularly, although at a slow rate. It seems not unlikely that friction was eventually overcome by a secretion of mucus sufficient to coat the rough edges of the bran.

The initial emptying of the stomach therefore appears to depend on two factors—the consistency of the meal and the presence of peristalsis of adequate depth.

*Further Progress of Evacuation*—A study of the tables will show that, after the initial emptying, the various meals left the stomach at widely different rates. These differences can, we think, be satisfactorily explained by the two factors,—the consistency of the meal, and the depth of the peristaltic waves.

The influence of the consistency of the meal is best illustrated by the behavior of the substances of little or no food value. Thus liquid paraffin left the stomach much more rapidly than bran, while agar occupied an intermediary position. As far as we know, these substances excite little gastric secretion, and hence their consistencies probably do not change appreciably in the stomach.

Many foodstuffs, such as meats and vegetables, excite a secretion of gastric juice. The consistency, and therefore the rate of evacuation, of a meal may thus undergo alteration in the stomach, not only from the presence of the gastric juice, but also from its digestive action.

The depth of the peristaltic waves was found to be shallow in the case of meals which contained fat. Two explanations of this difference present themselves, the fatty acids of fat digestion may irritate the duodenum and affect peristalsis through nerve impulses, as suggested by Barsony and Hortobagyi,<sup>15</sup> or some product of fat digestion circulating in the blood may depress muscular activity and influence the depth of the waves. The latter explanation appears to receive support from



observations on hunger contractions of the stomach. Thus Farrell and Ivy<sup>31</sup> found that fat put into a dog's stomach inhibited the contractions of a stomach pouch which had been completely separated from the stomach and implanted in a new position just under the skin.

In two experiments a large meal of cream was taken seven and one half hours before a meal of thick porridge and barium, the idea being that intestinal absorption of fat would be in full course (Leathes and Raper<sup>32</sup>), although the stomach was empty. The progress of these meals of porridge was definitely slower than that of similar meals taken without the previous ingestion of cream. These observations appear to support the hypothesis that peristalsis of the stomach may be depressed by products of fat digestion circulating in the blood. We cannot, however, rule out the possibility that impulses from the jejunum or ileum were operating to depress peristaltic activity.

#### SUMMARY

1 The initial emptying of the stomach depends on two factors,—the presence of peristalsis of adequate depth, and the consistency of the meal.

2 All liquid meals start to leave the stomach as soon as ingested, regardless of their composition. Most solids commence to leave the stomach as soon as they reach the pyloric sphincter.

3 After the first few minutes, proteins are evacuated more slowly than carbohydrates, and fats are slowest of all.

4 In the case of fats this delay is associated with shallower peristaltic waves, due possibly to depression of muscular activity by products of fat digestion circulating in the blood.

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31 Farrell, J. I., and Ivy, A. C. *Am J Physiol* **76** 227, 1926.

32 Leathes, J. B., and Raper, H. S. *The Fats*, London, 1925, p. 134.

# BLOOD PRESSURE IN DIABETES MELLITUS

## A STATISTICAL STUDY<sup>\*</sup>

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MINNEAPOLIS

The subject of blood pressure in diabetes mellitus has aroused considerable controversy during recent years, and yet there is no unanimity of opinion on the matter at the present time. With the discrepancies in the literature in mind, a statistical study of the problem has been undertaken. Obviously, in order to make such a study, some standard must be used for comparison. In the analysis of the data presented in this paper the blood pressures of the diabetic persons are compared with those of three control series: (1) a group of dispensary patients, (2) a group of hospital patients, and (3) a so-called normal group. A necropsy series of diabetic cases is also studied.

## LITERATURE

In 1733, Stephen Hales<sup>1</sup> performed his memorable experiment on the blood pressure of the horse, in which, after the insertion of a brass pipe into the crural artery, the "blood rose in the tube eight feet three inches perpendicular above the level of the left ventricle of the heart." In 1828, Poisseulle<sup>2</sup> introduced the mercury manometer as a means of recording blood pressure, and in 1847 Ludwig combined the mercury and the graphic methods, so that permanent records of the blood pressure were available.

Little was done on the blood pressure of man, however, until 1896, when Riva-Rocci<sup>3</sup> devised the armlet method for taking pressures, and the knowledge of human blood pressure dates from that time. In the subsequent year, Hill and Bernard<sup>4</sup> devised a similar method. In this early work the width of the armlet of the blood pressure apparatus was variable, although it is now known that the blood pressure varies with armlets of different widths. In 1901, however, von Recklinghausen<sup>5</sup> standardized the width of the cuff. Thus, the knowledge of

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<sup>\*</sup> Abstract of Master's Thesis, Department of Pathology, University of Minnesota, E T Bell, M D, Advisor.

1 Hales, Stephen. Statistical Essays Containing Hemostatics, London, 1733.

2 Poisseulle, quoted by Tigerstedt. Lehrbuch Physiologie des Kreislaufes, Leipzig, S Hirzel, 1893, p 322.

3 Riva-Rocci, S. Gazz med di Torino 47 981, 1896.

4 Hill, L, and Bernard, H. Brit M J 2 904, 1897.

5 Von Recklinghausen, H. Arch f exper Path u Pharmakol 46 78, 1901.

blood pressure in man really dates from the beginning of the present century, although Vierordt, Marey, Basch and Allbutt, abroad, and Eilanger, Cook, Janeway and many others, in this country, had been working on the problem

The question arises as to which sounds one should take as representing the points at which the systolic and the diastolic readings should be made. I am cognizant of the fact that there is sometimes an auscultatory gap (*trau auscultatoire* of the French), in which the first sound appears, disappears and latter reappears as the pressure in the cuff is diminished. This silent phase is most prone to be present in cases of hypertension, and the upper limit of sound is apt to be unobserved unless the pressure in the cuff is elevated to approximately 200 mm of mercury. Tixier<sup>6</sup> first described this phenomenon in 1918, and in the following year Tixier and Gallavardin<sup>7</sup> observed the silent gap in a case of aortic stenosis. Gibson<sup>8</sup> described the five zones which are observed in taking blood pressures as follows. The first zone is of short duration and is sometimes difficult to detect, since the sounds are soft and dull, in the second zone, which extends over a range of from 20 to 60 mm of mercury, the quality of the sounds is variable, and it is in this phase that the silent gap occurs when present. The third zone is the most distinctive phase, and here the sounds are loud and snapping and increase in intensity to a maximum, when they suddenly change to the fourth zone, this zone is of short duration, and here the sounds are soft and dull. In the fifth zone, the sounds disappear. The point at which the first sound is heard in the first zone represents the systolic pressure, and the sudden change in the character of the sounds in the fourth zone marks the point at which the diastolic pressure should be taken.

The pressures obtained by the oscillation method are higher than those determined by either the palpation or the auscultation method, and are less accurate than the readings obtained by the use of the combined methods. Consequently, the combined method has been used in obtaining the data for the present paper.

What should be considered as the normal blood pressure? A voluminous literature has accumulated on this subject. I am chiefly concerned with the blood pressure in the older age groups, but Burlage,<sup>9</sup> Melvin and Murray,<sup>10</sup> Addis<sup>11</sup> and Conception and Bulatao<sup>12</sup> found

6 Tixier, L. *Paris med* **27** 502, 1918

7 Tixier, L, and Gallavardin, L. *Arch d mal du coeur* **12** 447, 1919

8 Gibson, P. C. *Lancet* **2** 1012, 1927

9 Burlage, S. R. *Proc Soc Exper Biol & Med* **19** 247, 1922

10 Melvin, G. S., and Murray, J. R. *J Exper Physiol* **15** 125, 1914-1915

11 Addis, T. *Blood Pressure and Pulse Rate Reactions*, *Arch Int Med* **30** 240 (Aug) 1922

12 Conception and Bulatao. *Philippine J Sc* **2** 135, 1916

that for the first three decades of life the average systolic blood pressures are well below 130 mm of mercury

As one advances to the older age groups, it is found that there is considerable controversy over the mean systolic blood pressures. Wiggers<sup>13</sup> stated that a value of from 100 to 125 mm of mercury by the palpation method may be taken as the normal systolic blood pressure before middle life, and that a value of perhaps 10 mm higher may be expected after that period.

Richter<sup>14</sup> found the average systolic pressure for persons between the ages of 62 and 89 to be 153 mm of mercury. Saller<sup>15</sup> found that the systolic pressure in women is higher than that in men in the older age groups, being more than 150 mm after the age of 56 in women, while the systolic pressure in men of the corresponding age group is 136 mm. Reilingh<sup>16</sup> expressed the belief that the average systolic pressure for persons over the age of 60 is 168 mm of mercury, and Wildt<sup>17</sup> found that the average pressure for persons of the same age group is 150 mm. Sachs<sup>18</sup> found the average systolic blood pressure in persons of 70 years or more to be 180 mm of mercury. Janeway,<sup>19</sup> Norris, Bazett and McMillan,<sup>20</sup> Hensen<sup>21</sup> and Goldscheider<sup>22</sup> suggested that 160 mm of mercury be taken as the upper limit of normal systolic blood pressure in older persons.

On the other hand, I found many articles in the literature in which the systolic blood pressures are much lower than those cited. Symonds,<sup>23</sup> in a study of 150,000 cases, divided into five-year age groups, found the highest systolic value to be 142 mm of mercury, and this pressure was found in the oldest age group. Woley,<sup>24</sup> in a series of 1,000 persons of all ages, found the average systolic pressure to be 127.5 mm for males and 120 for females. Fisher<sup>25</sup> reported the highest systolic

13 Wiggers, C. J. *Modern Aspects of Circulation in Health and Disease*, Philadelphia, Lea & Febiger, 1923, p. 359.

14 Richter, A. *Deutsches Arch f klin Med* **148** 3, 1925.

15 Saller, K. *Ztschr f d ges exper Med* **58** 683, 1928.

16 Reilingh, quoted by Sachs, H. *Jahresk, f arztl Fortbild* **18** 20, 1927.

17 Wildt, H. *Zentralbl f Herzkrankh* **4** 41, 1912.

18 Sachs, H. *Jahresk f arztl Fortbild* **18** 20, 1927.

19 Janeway, T. C. *A Clinical Study of Hypertensive Cardiovascular Disease*, *Arch Int Med* **12** 755 (Dec) 1913.

20 Norris, G. W., Bazett, H. C., and McMillan, T. M. *Blood Pressure Its Clinical Applications*, Philadelphia, Lea & Febiger, 1927.

21 Hensen. *Deutsches Arch f klin Med* **67** 438, 1900.

22 Goldscheider, quoted by Sachs, H. *Jahresk f arztl Fortbild* **18** 20, 1927.

23 Symonds, B. *Blood Pressure of Healthy Men and Women*, *J A M A* **80** 232 (Jan 27) 1923.

24 Woley, A. P. *The Normal Variation of the Systolic Blood-Pressure*, *J A M A* **55** 121 (July 9) 1910.

25 Fisher, J. W. *The Diagnostic Value of the Sphygmomanometer in Examinations for Life Insurance*, *J A M A* **63** 1752 (Nov 14) 1914.

pressure in the 56 to 60 year group, in which the pressure was 135 mm of mercury Dunham,<sup>26</sup> in 8,645 apparently normal soldiers, found the highest systolic pressure in the 50 to 64 year group, in which it was 134 mm of mercury

That there is a positive correlation between systolic blood pressure and increase in body weight above normal is shown by the work of Dunham,<sup>26</sup> Dublin Fisk and Kopf,<sup>27</sup> Faber<sup>28</sup> and Symonds<sup>23</sup>

Before entering into a discussion of the literature on the subject of the blood pressure in diabetes mellitus, I shall mention a few articles which have been published pertaining to the relation between blood pressure and blood sugar levels Hopkins<sup>29</sup> and Frank<sup>30</sup> found that a moderate hyperglycemia occurs in many cases of hypertension Neubauer<sup>31</sup> and Botti<sup>32</sup> also noted a relationship existing between hyperglycemia and high blood pressure O'Hare<sup>33</sup> and Kylin<sup>34</sup> showed the relation between hypertension and low carbohydrate tolerance Hopkins<sup>29</sup> concluded that four clinical features occur together hypertension, hyperglycemia, arteriosclerosis and obesity Harle<sup>35</sup> failed to find any exact parallelism between the blood sugar and the blood pressure curves, although one fourth of his cases showed a moderate hyperglycemia Peiser,<sup>36</sup> on the other hand, found no elevation of the blood sugar level in cases of hypertension uncomplicated by diabetes mellitus

The literature is divided in regard to the question of the blood pressure in diabetes mellitus Vaquez,<sup>37</sup> Orr,<sup>38</sup> Kahn,<sup>39</sup> Janeway<sup>40</sup> and Elliot<sup>41</sup> expressed the belief that the systolic blood pressure is not elevated in uncomplicated cases of diabetes Rosenbloom<sup>42</sup> also sub-

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26 Dunham, G C *Internat Clin* **3** 81, 1925

27 Dublin, L I, Fisk, E L, and Kopf, E W *Am J M Sc* **170** 576, 1925

28 Faber, A *Skandin Arch f Physiol* **45** 189, 1924

29 Hopkins, A H *Am J M Sc* **149** 254, 1915

30 Frank, E *Deutsches Arch f klin Med* **103** 397, 1911

31 Neubauer, E *Ztschr Biochem* **25** 284, 1910

32 Botti, A *Polichinico* **29** 249, 1922

33 O'Hare, J P *Am J M Sc* **160** 366, 1920

34 Kylin, E *Zentralbl f inn Med* **42** 783, 1921, *ibid* **44** 81, 1923

35 Harle, F *Ztschr f klin Med* **92** 124, 1921

36 Peiser, F *Ztschr f klin Med* **106** 290, 1927

37 Vaquez, H *Gaz d hop* **78** 1221, 1904

38 Orr, Montana M J **31** 833, 1902

39 Kahn, Max *Angina Pectoris of Diabetes*, J A M A **76** 570 (Feb 26) 1921

40 Janeway, T C *Bull Johns Hopkins Hosp* **26** 341, 1916

41 Elliot, A R *A Clinical Study of Blood Pressure Variations in Diabetes and Their Bearing on the Cardiac Complications*, J A M A **49** 27 (July 6) 1907

42 Rosenbloom, J *J Lab & Clin Med* **7** 392, 1922

scribed to this view, although in his series a systolic pressure of 150 mm or more was found in 40 per cent of the cases; of 170 mm or more in 17 percent and of 200 mm or more in 12 per cent. Adams<sup>43</sup> and Kahn<sup>39</sup> expressed the opinion that when hypertension is present in persons affected with diabetes mellitus the elevated blood pressure is suggestive of the presence of some other condition, which is of itself producing the hypertension.

On the contrary, many investigators believe that the blood pressure in diabetic persons tends to be elevated. Potain<sup>44</sup> found that the blood pressure in diabetes is even higher than in nephritis. Joslin<sup>45</sup> stated that in patients affected with diabetes mellitus the blood pressure tends to be below normal in those under the age of 35, after which it is slightly above normal. He stated, "The interval between diabetic and normal widens as age advances." Bell and Clawson<sup>46</sup> found that 42.5 per cent of the patients with diabetes in their series had a systolic blood pressure of 150 mm of mercury or more, and they concluded that hypertension is 2.7 times as frequent in diabetic as in nondiabetic persons over 50 years. Peterson,<sup>47</sup> in a study of the arterioles of the kidney and of the pancreas, found more marked arteriosclerosis in the diabetic group than in his control series. Kramer,<sup>48</sup> in a study of 500 cases of diabetes mellitus, found a systolic pressure of 150 mm of mercury or more in 39 per cent. He concluded, "The combination of hyperglycemia and hypertension occurs so frequently that it has ceased to be looked upon as a coincidence." Katz-Klein,<sup>49</sup> in a series of 120 cases of diabetes, found a systolic blood pressure of 160 mm of mercury or more in 25 per cent. She stated, however, that the blood sugar and the blood pressure curves do not run parallel. Crummer<sup>50</sup> also observed that hypertension is common in cases of diabetes, while Maranon<sup>51</sup> expressed the belief that a high systolic blood pressure may be present prior to the onset of the disease, but tends to fall during its course.

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43 Adams, S. F. Proc. Staff Meetings Mayo Clinic **3** 303, 1928.

44 Potain, quoted by Allbutt. Diseases of the Arteries, Including Angina Pectoris, New York, The Macmillan Company, 1915, vol. 1.

45 Joslin, E. P. Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1923.

46 Bell, E. T., and Clawson, B. J. Primary (Essential) Hypertension, Arch. Path. **5** 939 (June) 1928.

47 Peterson, R. F. University of Minnesota Thesis, June, 1927.

48 Kramer, D. W. Am. J. M. Sc. **176** 23, 1928.

49 Katz-Klein, F. Med. Klin. **20** 1808, 1924.

50 Crummer, M. Herald **21** 46, 1902.

51 Maranon, G. Zentralbl. f. inn. Med. **43** 169, 1922, Arch. de cardiologie y Hematol. **125** 3, 1922.

## STATISTICAL STUDY

In a study of normal blood pressure the consideration of primary importance is to secure normal material. This seems evident, and yet it is surprising to note the number of studies which have been reported in which the blood pressures were assumed to represent normal values, although the subjects on whom the data were accumulated were ill.

In the so-called normal group discussed in this paper the subjects included visitors to the hospital and the personnel of the hospital. Obviously, the greater number of these persons were practically normal.

The instrument used in taking the blood pressures was a Baumanometer with a cuff of standard width. The accuracy of the instrument was checked against two similar instruments before the work was begun, and in all cases care was taken to have the mercury level at zero prior to the elevation of the pressure in the cuff. Although Hill and Rowland<sup>52</sup> found that the blood pressure is practically the same in

TABLE 1—*Age Distribution in Four Series of Cases*

Age Groups	Normal	Dispensary	Hospital	Diabetic
35-40	57	43	56	18
40-45	50	43	69	30
45-50	55	43	42	44
50-55	54	43	69	52
55-60	54	44	52	84
60-65	61	43	46	59
65-70	57	36	54	31
70-75	61	28	41	22
75 plus	60	33	43	8

the lower and upper extremities normally, care was taken to apply the cuff in approximately the same position in all cases, this being about 2 inches (5 cm.) above the fold of the antecubital space. The pressure in the cuff was elevated to 200 mm. of mercury and gradually lowered, care being taken to observe the auscultatory gap, if present. Prolonged compression by the cuff was avoided, since MacWilliam<sup>53</sup> and others have shown that the continued pressure may modify the readings obtained by the auscultation method. In all cases the palpation and the auscultation methods were combined, as recommended by MacWilliam and Melvin,<sup>54</sup> and the pressure obtained by the former method was constantly less than that obtained by auscultation. The subjects were all observed while in the sitting posture, the readings were taken approximately two hours after meals, and in no case was the blood pressure taken until the subject had been given a rest period. Unfortunately, in the majority of cases only one observation was made. The blood pressures were all taken by me.

52 Hill, L., and Rowland, R. A. *Heart* 3 222, 1912

53 MacWilliam, J. A. *Physiol Rev* 5 303, 1925

54 MacWilliam, J. A., and Melvin, S. *Brit M J* 1 693, 1914

Three control groups were studied, and the blood pressures in each of these were compared with the pressures in the diabetic series. The first control group consisted of 356 dispensary patients, all of whom were 35 years or older. These were consecutive cases, taken regardless of the conditions for which the patients were being treated. In the second control series the blood pressures in 472 consecutive hospital cases were studied. Again, these cases were taken regardless of the complaint of the patient. In the third control series blood pressures were taken on apparently normal persons, the pressure being taken according to the methods already outlined.

TABLE 2—*Mean Systolic and Diastolic Blood Pressures in Dispensary Series by Age Groups and by Sex*

Age Groups	Males		Females		Composite	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
35-40	135	86	129	83	132	84
40-45	136	89	134	85	135	87
45-50	144	85	139	82	142	84
50-55	135	82	131	79	134	81
55-60	151	90	145	87	149	89
60-65	148	87	145	83	147	85
65-70	154	86	154	84	155	85
70-75	155	86	152	82	154	84
75 plus	156	95	160	94	158	95

TABLE 3—*Mean Systolic and Diastolic Blood Pressures in Hospital Series by Sex and by Age Groups*

Age Groups	Males		Females		Composite	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
35-40	127	78	123	75	124	76
40-45	123	85	121	80	120	83
45-50	155	86	149	78	152	82
50-55	151	88	145	86	147	87
55-60	155	86	152	85	153	85
60-65	151	86	154	88	152	87
65-70	146	85	140	79	143	82
70-75	155	93	150	89	152	91
75 plus	148	98	142	86	146	87

In table 1 the age group distribution for these three series, as well as for the diabetic series, is given. In tables 2, 3 and 4 the average systolic and diastolic blood pressures are shown, arranged according to sex and according to age groups.

In the 500 clinical cases of diabetes mellitus, 408 of the patients were 35 years or older, only the older age groups will be used in the statistical study which is to follow. Of these 408 patients, 356 received more than one observation on the blood pressure. If more than one reading was made, the mean pressure was taken in computing the statistical data given in the present paper. All the observations were made according to the methods described except that in this group the



readings were made by several different persons. The blood pressures of this group are shown in table 5, arranged according to sex and age distribution.

In all four groups there were more females than males, and the proportion was greatest in the diabetic series, the ratio being 5:3.

In table 2 it will be seen that in the dispensary series the mean systolic blood pressure of the men was greater than that of the women in all age groups except the 65 to 70 and 75 year groups, whereas the diastolic pressures of the males were higher in all age groups. In the hospital series, as shown in table 3, both the systolic and the

TABLE 4—*Mean Systolic and Diastolic Blood Pressures in Normal Series by Sex and by Age Groups*

Age Groups	Males		Females		Composite	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
35-40	124	83	118	77	120	79
40-45	130	80	126	76	129	79
45-50	135	84	133	82	134	83
50-55	133	85	130	82	131	83
55-60	142	91	137	86	139	88
60-65	145	87	136	79	141	89
65-70	139	82	135	78	137	80
70-75	148	90	141	82	144	87
75 plus	140	80	131	69	135	75

TABLE 5—*Mean Systolic and Diastolic Blood Pressures in Diabetic Series by Sex and by Age Groups*

Age Groups	Males		Females		Composite	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
35-40	112	72	129	76	118	73
40-45	118	71	138	85	125	76
45-50	116	76	151	84	137	81
50-55	138	82	155	85	144	83
55-60	135	81	159	85	149	82
60-65	148	89	153	82	152	85
65-70	138	84	178	89	154	85
70-75	151	83	169	86	159	84
75 plus	176	96	120	69	136	76

diastolic blood pressures were higher in the case of the women in the 60 to 65 year age group, while the pressures of the men were higher in all the other age groups. In the normal series, as shown in table 4, both the systolic and the diastolic blood pressures were higher in the males in all age groups. In the diabetic series, as shown in table 5, it was found that the systolic blood pressures were higher in the women than in the men after the age of 35, with the exception of the 75 year age group, and the diastolic pressures of the women were higher than the diastolic blood pressure in the men in the corresponding age groups, with the exception of the 60 to 65 year age group, in which the mean diastolic pressure was higher in the men than that in the women.

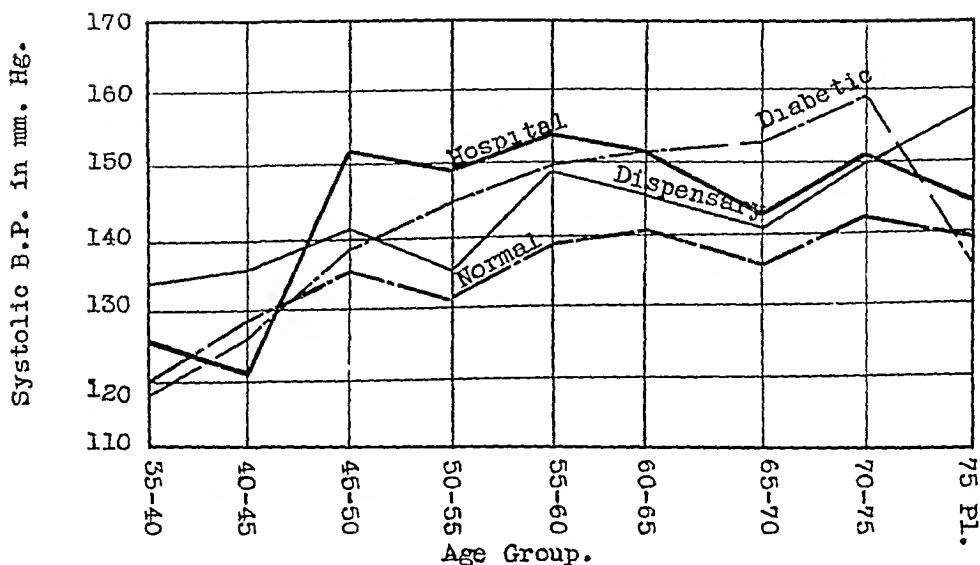


Chart 1—Curves for the mean systolic blood pressure of the different series by age groups

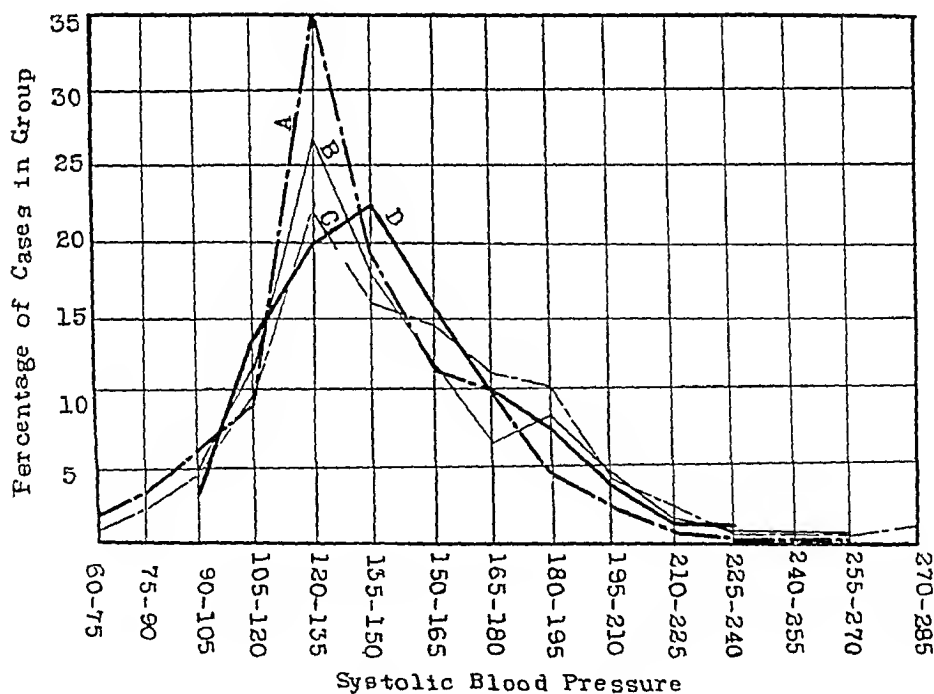


Chart 2—Distribution of cases according to the systolic blood pressure (15 mm groups) in persons over 35. A indicates the curve for the normal series, B, for the hospital series, C, for the dispensary series, and D, for the diabetic series

If tables 2, 3, 4 and 5 are compared, it is seen that the mean systolic blood pressure was higher in the diabetic series than that of any other series in only two age groups, the 65 to 70 and the 70 to 75 year groups, while the diastolic pressure was not higher in the diabetic series than that of any other series in any single age group. It was also found that in the normal series the systolic pressures were lower than those of any other group of cases after the age of 45, whereas the diastolic pressures were lower in the 60 to 65, 65 to 70 and 75 year age groups. The mean systolic blood pressures in the different series are represented by age groups in chart 1.

Arranging the cases in 15 mm groups according to their systolic blood pressures, so as to obtain smoother curves, it was found that the peak of the curve for the diabetic series came in the 135 to 150 mm

TABLE 6—*Percentage of Cases in Each Series by Age Groups with Systolic Pressure of 150 mm or More, and with Diastolic Pressure of 100 mm or More*

Age Groups	Normal		Dispensary		Hospital		Diabetic	
	Systolic 150 Plus	Diastolic 100 Plus	Systolic 150 Plus	Diastolic 100 Plus	Systolic 150 Plus	Diastolic 100 Plus	Systolic 150 Plus	Diastolic 100 Plus
35-40	18	18	20.9	16.3	3.6	5.4	5.5	
40-45	19.0	2.1	25.5	18.6	26.1	17.4	25.8	20.0
45-50	29.1	18.2	23.2	16.3	33.1	23.8	29.9	15.9
50-55	25.5	9.9	47.5	4.6	40.6	24.7	38.6	19.5
55-60	36.4	18.2	45.5	27.0	48.1	32.7	45.0	22.6
60-65	40.0	6.9	51.2	18.6	47.9	21.8	52.0	12.8
65-70	29.1	5.4	55.5	16.2	50.0	18.5	58.0	25.8
70-75	32.2	13.6	57.2	35.6	51.2	21.9	77.0	18.2
75 plus	30.0	11.6	54.6	30.3	41.9	18.6	58.1	12.5

group, whereas the peaks of all the other curves fell in the 120 to 135 mm group (chart 2). It was also noted that subsequently the curve for the diabetic series was higher than any other curve, until it was finally crossed by the curve for the dispensary series at about 160 mm of mercury.

In table 6 the percentage of cases in each group with a systolic blood pressure of 150 mm or more, and with a diastolic blood pressure of 100 mm or more, is shown according to age groups. From the study of this table it is evident that in the four highest age groups a greater percentage of cases having systolic blood pressures of 150 mm or more was found in the diabetic series than in any other series, while only in the 65 to 70 year age group was the percentage of cases having a diastolic pressure of 100 mm or more higher in the diabetic series than in any other series.

Investigation of the pulse pressure is an important consideration in such a disease as diabetes mellitus, in which arteriosclerosis is a too

frequent complication to be overlooked Fahr<sup>55</sup> showed that "arteriosclerosis only increases the work of the heart insofar as it necessitates increased blood pressure" With an elevation of systolic and of diastolic blood pressure, more work is required of the heart to expel a given volume of blood than with normal systolic and diastolic blood pressures as has been shown by Bramwell, Downing and Hill<sup>56</sup> Under these conditions a higher pulse pressure is required In the present series of cases it was found that the pulse pressure was higher in the diabetic series than in any other group of cases in the following age groups 50 to 55, 60 to 65 and 70 to 75

In curves representing the distribution of cases in the different age groups it was found that the curves were asymmetrical However, by the use of the formula given by Karl Pearson, the skewness of the curves was estimated for the different series of cases The values were found to be as follows dispensary series, 0.276, hospital series, 0.319, normal series, 0.045, and diabetic series, 0.004 Thus, it is seen that the age distribution of the cases was most asymmetrical in the dispensary and hospital series

The mean systolic blood pressure for the entire group in each series was determined, regardless of age and sex, and the following values were found dispensary series, 143 mm, hospital series, 144 mm, normal series, 136 mm, and diabetic series, 144 mm The mode for the different series was dispensary, 132.5 mm, hospital, 132.5 mm, normal, 122.5 mm, and diabetic, 142.5 mm The median was as follows dispensary, 142.5 mm, hospital, 137.5 mm, normal, 132.5 mm, and diabetic, 142.5 mm Thus, the mean systolic blood pressure for the dispensary, hospital and diabetic series was practically the same, whereas that for the normal series was considerably less than that of any other group

Before proceeding further into a statistical consideration of this problem it will be necessary to calculate the standard deviation for systolic blood pressure in each of the four groups of cases, since further determinations will involve a consideration of these values In statistical work the root-mean square of a series of numbers is the square root of the arithmetic mean of their squares In applying this formula to the systolic blood pressures the following values for the standard deviation were found

Dispensary series	38.0
Hospital series	32.9
Normal series	29.6
Diabetic series	44.2

55 Fahr, G Proc Soc Exper Biol & Med **24**.405, 1926

56 Bramwell, J C, Downing, A C, and Hill, A V Heart **10** 289, 1923  
Bramwell, J C, and Hill, A V Lancet **1** 891, 1922

Having obtained the standard deviation for the systolic blood pressures, the probable error for each of these values remains to be determined. These are as follows:

Dispensary series	$38.0 \pm 1.32$
Hospital series	$32.9 \pm 1.01$
Normal series	$29.6 \pm 0.89$
Diabetic series	$44.2 \pm 1.47$

From the data thus far obtained the coefficient of variability was calculated. This is the ratio of the standard deviation to the arithmetic mean, and is usually expressed as a percentage. These values are shown in the following:

Dispensary series	26.6
Hospital series	22.9
Normal series	21.8
Diabetic series	30.7

From the data given the significance of these figures can be determined. In statistical work the significance is based on the ratio of the difference of the means to the probable error of the difference. The ratios are:

Diabetic and hospital series	0.0
Diabetic and dispensary series	0.5
Diabetic and normal series	4.7
Normal and hospital series	5.9
Normal and dispensary series	4.4

Statisticians are accustomed to take arbitrarily the ratio of 2.5 or 3, or more, as a significant value. Hence, the ratio of the difference of the means to the probable error of the difference was significant in the normal and diabetic series, in the normal and hospital series and in the normal and dispensary series.

Thus far the standard deviation and the probable errors for the systolic blood pressures for the entire groups have been studied. In computing the standard deviation and the probable errors of the mean systolic blood pressures for each age group in the normal and in the diabetic series, the ratio of the difference of the means to the probable error of the difference of the means was found to have a significant value (2.5 or more) in the following age groups: 50 to 55, 55 to 60, 60 to 65, 65 to 70 and 70 to 75. The ratio was not significant in the younger age groups, nor was it significant in the 75 year age group. The discrepancy in the latter case was probably due to the small number of cases in this group.

It is obvious that some attempt should be made to correlate age and systolic blood pressure in the different series of cases. The correlation was positive in all the different groups of cases, and was highest in the normal series, while it was lowest in the dispensary series and in the hospital series. The values are as follows:

Dispensary series	0.0409
Hospital series	0.0755
Normal series	0.2659
Diabetic series	0.2238

The probable error of the coefficient of correlation of age and systolic blood pressure was determined in the normal and in the diabetic series, and these values are:

Normal series	$0.2659 \pm 0.0277$
Diabetic series	$0.2238 \pm 0.0316$

It was found, therefore, that the difference of the coefficients of correlation bore a ratio to the probable error of the difference of 1:10, which is a highly significant value.

From the data given straight line curves were plotted for the different groups of cases, by the use of a regression formula. These curves are shown in chart 3. It is seen that the curves for the dispensary and hospital series show little elevation, owing to the low correlation between age and systolic blood pressure. It is also evident that the curve for the normal group is definitely lower than any of the other curves, and that after the age of 60 the curve for the diabetic series is higher than any other curve.

In addition to the study of blood pressure, it is pertinent that other evidence of hypertension be sought. It is conceivable that the blood pressure may have been within normal limits at the time the observations were made, although the person may have suffered from hypertension at some earlier period. It is known that changes in the small vessels are a more reliable index to hypertension than are changes in the larger vessels. Fortunately, the ocular fundi afford an excellent opportunity for the study of such vessels.

In the diabetic series the eyegrounds were examined in 386, or 77 per cent, of the cases. The points observed in these examinations were: abnormal tortuosity of the vessels, caliber changes of the vessels, nicking at the arteriovenous junctions and areas of old or of recent hemorrhage. In 189 cases (38 per cent), some degree of vascular change was noted. Such cases were more frequent in the older age groups, although a few of the cases in the younger age groups also revealed some vascular injury.

In the diabetic series only 14 patients (2.8 per cent) were thought to have renal disease. Of the 500 cases, 239 (48 per cent) showed arteriosclerosis of varying degree.

No attempt has been made to determine the correlation between systolic blood pressure and increase in body weight above normal, since the weights were not available in the diabetic series.

In addition to the clinical series discussed, a group of diabetic cases coming to necropsy has been studied. Here the points of chief concern were the weight of the heart and kidneys and the cardiovascular complications.

As a standard for comparison, the weight of the heart in 1,000 consecutive necropsies was taken, the cases being arranged according

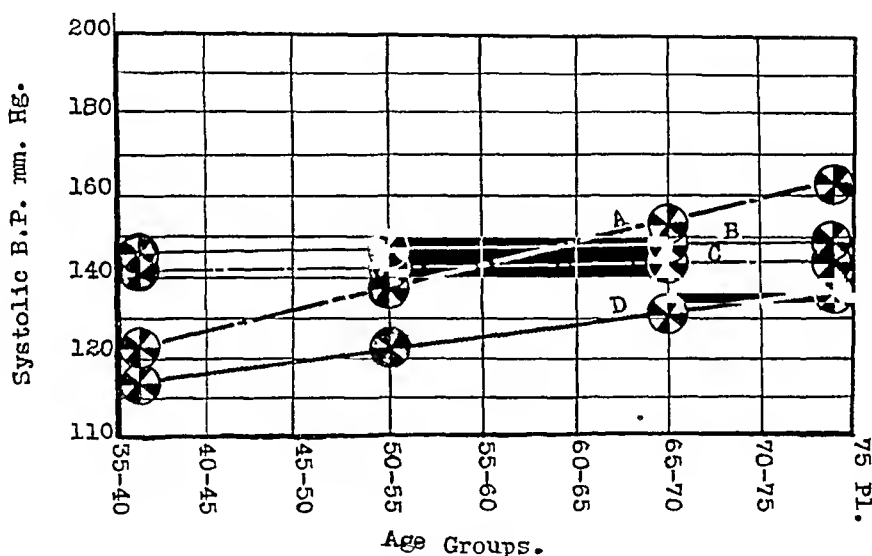


Chart 3—Straight line curves for the systolic pressures. *A* indicates the curve for the diabetic series, *B*, for the hospital series, *C*, for the dispensary series, and *D*, for the normal series.

to five-year age groups and according to sex. The mean values obtained showed that the heart tended to increase in size to about the age of 60, after which it decreased slightly. The highest mean weight in the men was 384 Gm., at the age of from 60 to 65, while the highest value in the women was 366 Gm., at the age of from 55 to 60.

In the study of 104 cases of diabetes mellitus coming to postmortem examination all cases showing vascular injury were excluded, since certain types of valvular disease may give rise to hypertrophy of the heart, there being no associated increase in systolic blood pressure. Of course, I was aware that other conditions than hypertension and valvular disease can cause hypertrophy of the heart. After calculating the mean weight, according to sex and also according to five-year age

groups, it was found that the weight of the heart of the men in the diabetic series exceeded that of the men in the control series after the 50 to 55 years age group, whereas the weight of the heart of the women in the diabetic series exceeded that of the women in the control series after the age of 65 to 70. When both sexes were included in this comparison, it was found that the curve representing the diabetic series was higher than that representing the control series after the age of 50 to 55, as shown in chart 4.

The weight of the kidneys was also studied, and a comparison made with the weight in a control group, the latter being based on the weight of the kidneys in 650 consecutive necropsies. It was found that the kidneys in the diabetic series weighed slightly more than those

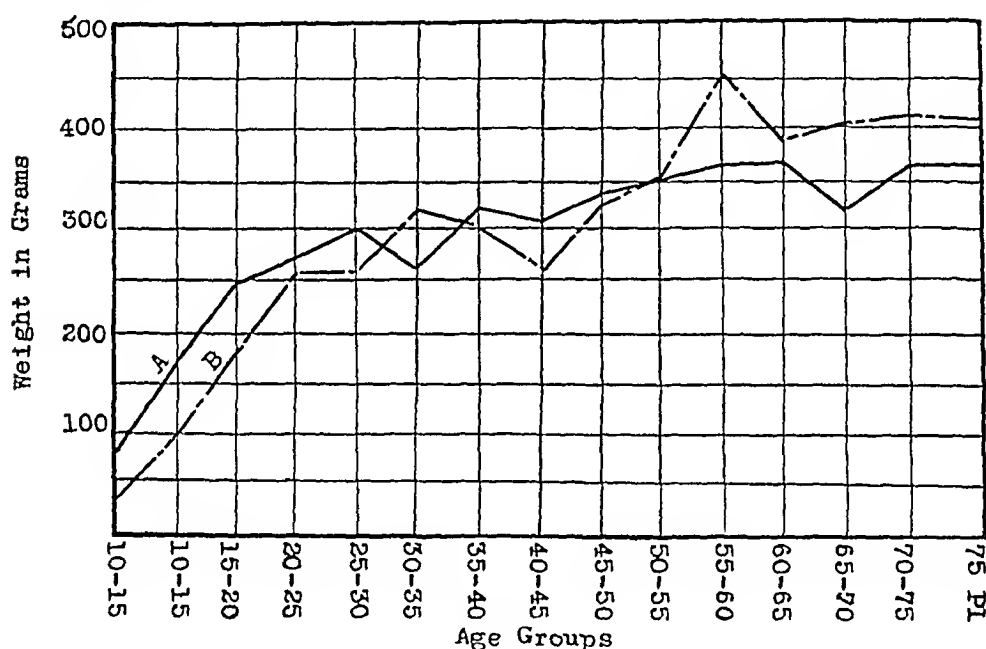


Chart 4—Curves for the weight of the heart for both sexes. *A* indicates the curve for the normal series, *B*, for the diabetic series.

in the control series. If hypertension were present in the diabetic cases, it might be expected that the kidneys in these cases would be the seat of arteriolar disease, and would be smaller than those in the control series. It should be remembered, however, that there is often an accompanying nephrosis, and in these cases the kidneys tend to be somewhat larger than normal.

The percentage of cases in which diagnoses pertinent to cardiovascular disease were made in the diabetic series is shown in the following tabulation:

General arteriosclerosis	32
Coronary sclerosis	22
Hypertrophy of the heart	21



Edema of the lungs	21
Gangrene of the extremities	19
Arteriosclerosis of the kidney	17
Chronic passive congestion of various viscera	15
Hydrothorax	13
Fibrous myocardium	10
Generalized edema	8
Ascites	6

#### SUMMARY

The blood pressure in a clinical series of cases of diabetes mellitus is compared with the blood pressure in a series of dispensary cases, with that in a series of hospital cases and finally, with that in a series of so-called normal persons. These figures are subjected to a statistical analysis.

A necropsy series of diabetic cases is also studied, and the weight of the heart and the kidneys is compared with the weight in a control series.

In elderly diabetic patients the systolic blood pressure is slightly higher than that of patients seen in a dispensary series or in a hospital series, and is considerably higher than the blood pressure in normal persons of the same age group.

Although the mean systolic blood pressure in the diabetic series is not essentially different from that in either the dispensary series or the hospital series, there is a greater tendency to a slight elevation of the systolic blood pressure in diabetic persons than in those in the other series mentioned, as is shown by a statistical study.

# THE RATE OF GLYCOLYSIS IN ERYTHREMIA (POLYCYTHEMIA VERA) \*

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AND  
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In a recent article by Falcon-Lesses,<sup>1</sup> the author applied the observations of Warburg and Murphy and Hawkins on glycolysis in malignant disease to the apparently similar problem of glycolysis in leukemic blood. He found that, whereas in normal persons glycolysis in blood containing not more than 100 mg of dextrose per hundred cubic centimeters is completed in about six hours, in the blood of patients with myelogenous leukemia the process was from two to three times as rapid, being complete in from one to four hours.

In seeking some explanation of the mechanism of this process, Falcon-Lesses made observations in two other cases showing abnormal conditions of the blood: one of polycythemia with a red cell count of 9,505,000 and a white cell count of 25,775 and the other a case of pernicious anemia with a red cell count of 2,800,000 and a white cell count of 4,000. The rate of glycolysis in the erythremic blood was "considerably accelerated," being complete in less than four hours. The rate of glycolysis in the blood of the patient with pernicious anemia was slower than in the normal blood. Falcon-Lesses suggested that the increase of white cells in the erythremic blood may be in part at least responsible for the increased rate but that "it seems more probable that the rates were in some manner dependent on the fact that the blood of one patient contains 6,000,000 more red cells per cubic millimeter than that of the other." This surmise seems logical, since it is known that glycolysis in normal blood is in the main a function of the intact red cells.

Having under observation at present two cases of erythremia, we thought it of interest to determine the rate of glycolysis under varying conditions, in particular to observe possible changes after the red blood cells had been brought down to approximately normal number by the administration of phenylhydrazine. One of these cases (no 2) seemed especially suitable for our purpose, since it belongs to the rather unusual type of erythremia in which the white cells are not increased, either

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\* From the Medical Service of the Jewish Hospital

1 Falcon-Lesses, M. Glycolysis in Normal and in Leukemic Blood, Arch Int Med 39 412 (March) 1928

originally or after the administration of phenylhydrazine, so that the question of glycolytic effect of the nucleated cells should not enter

The glycolysis experiments were carried out with defibrinated blood in order to preclude the inhibiting effect of the common anticoagulants. Immediately after defibrination, the blood samples were quickly warmed to 37 C in a water bath of constant temperature. Sedimentation of the cells was prevented by gentle agitation of the samples. The duration of the observation in no case exceeded a period of three hours, rendering special precautions of aseptic handling unnecessary.

#### REPORT OF CASES

CASE 1—Mrs. A, aged 59, has been under observation because of erythremia since November, 1922. She had had a number of courses of phenylhydrazine

TABLE 1—*Rate of Glycolysis in Case 1 on May 16*

Time of Incubation, Minutes	Sugar Content, Mg per 100 cc	Loss of Sugar, Mg per 100 cc
0	97	0
30	59	38
60	31	66
120	15	82

TABLE 2—*Rate of Glycolysis in Case 1 on June 27*

Time of Incubation, Minutes	Sugar Content, Mg per 100 cc	Loss of Sugar, Mg per 100 cc
0	89	0
30	58	31
60	15	74

since that date but none since December, 1926. On May 16, 1928, the blood showed the following: hemoglobin (Sahl), 116 per cent, red cells, 7,950,000, white cells, 16,100. The rate of glycolysis is shown in table 1.

The whole of the dextrose was cleaved in less than two hours, and it seems probable that during the second hour considerably more would have been broken down if it had been present. (The 15 mg per hundred cubic centimeters found at the end of the second hour represents reducing substances other than sugar<sup>2</sup>). Thus in judging the rate of glycolysis, one has to depend on the observation in the first hour, which shows a rate of 66 mg per hundred cubic centimeters of blood per hour.

The patient was then given phenylhydrazine, 0.06 Gm three times daily, until on June 20, 1928, she had taken a total of 3.4 Gm, and the blood showed hemoglobin, 93 per cent, red blood cells, 5,120,000, and white blood cells, 28,800. A week later, without further administration of the drug, the blood showed hemoglobin, 72 per cent, red blood cells, 3,600,000, white cells, 29,000. Blood was at this time again taken for determination of the rate of glycolysis.

<sup>2</sup> Somogyi, M. Reducing Non-Sugars and True Sugar in Human Blood, *J Biol Chem* 75 33, 1927.

The loss of sugar by glycolysis in this sample was 74 mg in one hour, the remaining 15 mg per hundred cubic centimeters again representing reducing substances other than sugar. Whereas the brief duration of the process does not permit the conclusion that the rate was higher in this case than in the first, it is fair to concede that it was at least not lower, a striking result, considering the difference of more than 100 per cent in the red counts of the two specimens.

CASE 2—J. G., a man, aged 49, was first seen on Dec 19, 1927, at which time his blood showed hemoglobin, 131 per cent, red blood cells, 8,900,000, and white blood cells, 6,400. Many subsequent counts during and after the administration of phenylhydrazine showed an average white cell count of about 8,000. A few counts were between 10,000 and 11,000.

On January 26, the blood showed red blood cells, 7,990,000, white blood cells, 7,600. The rate of glycolysis is shown in table 3.

TABLE 3—*Rate of Glycolysis in Case 2 on January 26*

Time of Incubation, Minutes	Sugar Content, Mg per 100 cc	Loss of Sugar, Mg per 100 cc
0	115	0
60	97	18
120	59	56
180	25	90

TABLE 4—*Rate of Glycolysis in Case 2 on March 9*

Time of Incubation, Minutes	Sugar Content, Mg per 100 cc	Loss of Sugar, Mg per 100 cc
0	112	0
30	94	18
60	76	36
90	57	55
120	39	73

The loss in dextrose was 90 mg in three hours, or 30 mg per hundred cubic centimeters of blood per hour, a rate about twice as high as in normal blood.

On February 1, the patient was given 0.05 Gm of phenylhydrazine three times daily, this dosage was later increased to 0.06 and 0.07 Gm three times daily. He did not remain under rigid observation and was probably a bit irregular in taking the drug but by March 9 had received a total of 5 Gm, when it was discontinued. The count at this time showed hemoglobin, 65 per cent, red blood cells, 4,080,000, and white blood cells, 8,400, the rate of glycolysis is shown in table 4.

The rate of glycolysis in this determination was 36 mg per hundred cubic centimeters of blood per hour, again slightly higher than it was before the red cell count had been decreased by approximately one half through the administration of phenylhydrazine.

Since in the instance of myelogenous leukemia it has been suggested on the basis of considerable evidence that the increased rate of glycolysis may be due to the presence of an increased proportion of young, newly formed white blood cells, we extended our investigation in this direction by repeating our experiments in case 2, with the addition of observations on the proportion of reticulated cells.

On Jan 14, 1929, the blood picture was hemoglobin, 160 per cent, red blood cells, 9,800,000, white blood cells, 8,720, and reticulated cells, 0.3 per cent. The rate of glycolysis is shown in table 5.

This represents a rate of glycolysis of 31 mg per hundred cubic centimeters per hour. The patient was then given 0.07 Gm of phenylhydrazine three times daily until by Feb 15, 1929, the rather large total of 6.8 Gm had been taken. On this date the hemoglobin was 90 per cent and the red blood cells 5,000,000. The administration of the drug was discontinued, and five days later, on February

TABLE 5—*Rate of Glycolysis in Case 2 on January 14*

Time of Incubation, Minutes	Sugar Content, Mg per 100 cc	Loss of Sugar, Mg per 100 cc
0	105	0
30	88	17
60	73	32
120	43	62
150	28	77

TABLE 6—*Rate of Glycolysis in Case 2 on February 20*

Time of Incubation, Minutes	Sugar Content, Mg per 100 cc	Loss of Sugar, Mg per 100 cc
0	80	0
30	63	17
60	47	33
90	31	49
120	18	62

TABLE 7—*Rate of Glycolysis in Case 2 on March 6*

Time of Incubation, Minutes	Sugar Content, Mg per 100 cc	Loss of Sugar, Mg per 100 cc
0	94	0
60	59	35
90	45	49
120	30	64
150	13	81

20, the following observations were recorded: red blood cells, 4,750,000, white blood cells, 12,500, and reticulated cells, 27 per cent, the rate of glycolysis is shown in table 6.

This table shows a rate of glycolysis of 31 mg per hundred cubic centimeters per hour, a value virtually identical with the one obtained before the reduction by one half of the red blood cells.

On March 6, the patient having received no phenylhydrazine meanwhile, this examination was repeated with the following result: red blood cells, 4,470,000, white blood cells, 9,700, and reticulated red cells, 1 per cent, the rate of glycolysis is shown in table 7.

The hourly rate of glycolysis in this instance was 32 mg per hundred cubic centimeters, or the same as in the preceding experiment. It should be remem-

bered that in the last two experiments the blood filtrates for sugar determinations were prepared by a new zinc-precipitation method,<sup>3</sup> which accounts for the fact that the initial level of the blood sugar is about 20 mg per hundred cubic centimeters lower than in the previous experiments on the same patient. All sugar determinations were carried out by the modified Shaffer-Hartmann method.

#### SUMMARY

1 The blood of patients with erythremia (polycythemia vera) shows a greatly increased rate of glycolysis.

2 This increased rate is independent of the red cell count as influenced by phenylhydrazine, and shows no direct relation to the proportion of young red cells, when the reticulated count is used as an index of such cells.

3 The increased rate of glycolysis in the usual case of erythremia is not dependent on the increased white count since the increased rate is also present with a low white cell count.

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<sup>3</sup> Somogyi, M. A Method for the Preparation of Blood Filtrates for Analysis, *Proc Soc Exper Biol & Med* **26** 353, 1929.

# THE BROMSULPHALEIN HEPATIC FUNCTION TEST

## REPORT OF A SERIES OF TESTS <sup>†</sup>

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Each of the numerous functions of the liver has been used, at one time or another, as an index to the function of the whole organ. The ideal test by which a quantitative estimation of one function of the liver may thereby indicate the degree of impairment in disease has not as yet been discovered. Although this criticism may be directed against any of the tests in use, it is not constructive. Only by repeated trial and experimentation can one hope to learn which tests are best suited to estimate the function of the organ in any given disease.

Perhaps the most infallible test is the clinical observation of jaundice, and of the concomitant changes in the excreta, namely, dark urine and clay-colored stools. Along with these clinical tests may be listed the laboratory tests which determine the amount of bilirubin in the blood, chief of which are the icterus index and the van den Bergh test. Shattuck, Brown and Preston,<sup>1</sup> in 1925, considered the icterus index as the most useful of all tests for this organ, but also stated that the Rosenthal test was of greater value in cirrhosis and malignancy, that it served as a guide to arsenical treatment in syphilis and that its greatest value was in hepatic disease without jaundice. Snell and Rowntree,<sup>2</sup> in 1928, considered that serum bilirubin was best studied by the van den Bergh test, although the icterus index afforded information of clinical significance.

Dextrose and fructose tolerance tests, estimation of bile and of dye in the feces and urine, estimation of bile and dye in the duodenal contents, together with many other tests, have been used. Much has been written and many cases reported with regard to the use of phenoltetrachlorophthalein. This dye given intravenously is normally removed from the blood in fifteen minutes, with the exception of from 3 to 5 per cent, and is all removed at the end of an hour. Retention is considered to indicate impaired hepatic function. This dye was irritant, caused occasional thrombosis and some severe local and general reaction, even though it was well diluted and the vein was well washed. In 1925,

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<sup>†</sup> Submitted for publication, May 25, 1929

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1 Shattuck, H F, Brown, J C, and Preston, M P. *Am J M Sc* **170** 510, 1925

2 Snell, A M, and Rowntree, L G. *Am J Surg* **4** 206 (Feb) 1928

Rosenthal and White<sup>3</sup> introduced a new dye which they had used experimentally in rabbits and then applied to clinical use. This was bromsulphalein (phenoltetrabromphthalein sodium sulphonate), and in twenty-five normal cases they found from 20 to 50 per cent of the dye remaining in the serum five minutes after intravenous injection, while there was none, or but a faint trace, remaining at the end of thirty minutes. The average five minute retention in the normal subjects was 35 per cent.

Maurer and Gatewood<sup>4</sup> had just previously quoted LeCount as suggesting the possibility of changes in the liver from the presence of any halogenated compound in concentrated form, due to the splitting off of the halogen acid in free form by the active metabolism of the liver with resultant acute necrosis. In reply to this, Rosenthal and White, in a footnote to their article just mentioned, said "The statement that the quantity of tetrachlorophthalein used may damage the liver has no foundation in a large amount of experimental work, and seems chemically impossible on a basis of the halogen content."

Greene, Snell, Walters<sup>5</sup> and others, in reporting a series of studies on hepatic function tests in 1925 stressed the parallelism between the bilirubin content and dye retention in hepatic disorders. In a later paper, Greene, McVicar, Rowntree and Walters<sup>6</sup> stated "We have stressed the close parallelism between the behavior of the serum bilirubin and the phenoltetrachlorophthalein in this series of cases. That the two readings do not have the same significance is shown by the behavior during the later portion of the recovery period." This point is also further borne out by the difference between the two tests in cirrhosis and carcinoma without jaundice.

Since the introduction of the new dye, bromsulphalein, the older dye has been generally discarded. A smaller quantity of bromsulphalein may be used yet a greater concentration results in the blood. No thromboses have been reported (except one in a case of polycythemia vera),<sup>7</sup> nor have there been any appreciable local or general reactions. Direct injection of a 5 per cent solution without further dilution is used, and samples for reading are taken at five and thirty minute intervals, thus simplifying the procedure.

Major William S. Shields was instrumental both in the use of tetrachlorophthalein and in the change to bromsulphalein at the Letterman

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3 Rosenthal, S. M., and White, E. C. Clinical Application of Bromsulphalein Test for Hepatic Function, *J. A. M. A.* **84** 1112 (April 11) 1925.

4 Maurer, S., and Gatewood, L. C. Phenoltetrachlorophthalein Liver Function Test, *J. A. M. A.* **84** 935 (March 28) 1925.

5 Greene, C. H., Snell, A. M., and Walters, W. Diseases of the Liver, *Arch. Int. Med.* **36** 248 (Aug.) 1925.

6 Greene, C. H., McVicar, C. S., Rowntree, L. G., and Walters, W. Diseases of the Liver, *Arch. Int. Med.* **36** 418 (Sept.) 1925.

7 Serby, A. M., and Bloch, L. *Am. J. M. Sc.* **176** 367 (Sept.) 1928.



General Hospital, and in February, 1928, use was made of the new dye Major Shields and Captain Douglas H. Mebane have selected most of the cases in which the test was applied, generally, I believe, with a view to study of the individual case, but always with an open mind as to the conclusions to be drawn pending a closer study of the test. Primarily, the first object in collecting the data in this series was to determine whether or not the five minute sample was of sufficient value to warrant its routine collection. To decide this question, it has been necessary to classify and group all cases in which the test was used, and the data thereby collected are presented for information. Apparent points of interest have been emphasized and some suggested conclusions drawn.

#### PROCEDURE

The test has been performed as follows

(a) The patient is prepared merely by having no breakfast. This is done to avoid the occasional cloudy serum obtained after a meal. In the future I expect to allow dry, unbuttered toast and coffee without cream.

(b) The patient's weight (stripped) is obtained, and this, divided by 55, gives the number of cubic centimeters of a 5 per cent solution of bromsulphalein to be injected. This is based on a dosage of 2 mg. per kilogram of body weight.

(c) The correct amount is injected into a large vein at the elbow, a 5 cc syringe graduated in tenths being used, and the injection completed in approximately one minute. At the beginning of the injection a stopwatch is started and the interval of injection noted.

(d) Five minutes after completion of the injection, a sample of blood is withdrawn from a vein of the other arm, to avoid possible residual dye.

(e) Another sample is withdrawn thirty minutes after completion of the injection.

(f) The blood is allowed to clot, the coagulum gently loosened, the sample centrifugated and the clear serum removed.

(g) To a portion of one sample of the serum a drop of 5 per cent hydrochloric acid is added and to another portion, three drops of a 10 per cent solution of sodium hydroxide. The other sample is treated only with the hydroxide. An alkaline tube is thus prepared for each sample, only one acid tube is required for each test.

(h) The acid tube is used as a serum control and behind it, in a comparator block, are placed the standards, as required. Behind each alkaline tube is a tube of distilled water. The tubes of permanent standards, as supplied by Hynson, Westcott and Dunning, are used to match the sample as nearly as possible. The experimenters interpolate when it is thought necessary.

The average normal reading, according to Rosenthal,<sup>3</sup> is 35 per cent at five minutes and zero at thirty minutes. In a recent number of the *American Journal of Medical Science*, Serby and Bloch<sup>7</sup> reported a series in which they used 35 as the upper limit of normal, but Rosenthal reported his normals to range between 20 and 50. Attention is called to the figures in the following tables which bear on this subject.

During approximately seven months (February 10 to September 13), 137 Rosenthal tests were performed, the bromsulphalein dye being used. In the 137 tests performed, no five minute sample could be obtained (or was not desired) in ten tests on nine persons. These tests were not included in the tables, except for three performed on patients whose other tests were complete. This gives a total of 130 tests in 100 cases. No effort was made at intensive study of these cases, other than as desired by the clinician. The laboratory personnel were generally uninformed as to the character of each case, and much of the data presented have been abstracted from charts after discharge of the patients. However, when a question of proper classification arose, an effort was made to avoid favoring the test by consultation with Captain Mebane, on whose service most of the patients were studied. From

TABLE 1—*Bromsulphalein Tests at Letterman General Hospital from Feb 10 to Sept 13, 1928*

Group	Cases	Tests
Hepatitis, nonsyphilitic and nonarsenical	5	16
Hepatitis, syphilitic and arsenical	10	19
Cancer	7	9
Cirrhosis		
Atrophic	1	2
Unclassified	5	5
Hypertrophic	19	25
Cholecystitis and cholelithiasis	11	11
Cholangitis	3	3
Nonhepatic	40	41
	<hr/> 101	<hr/> 131
Correction for one case duplicated under malignancy and cirrhosis, hypertrophic	1	1
Total	<hr/> 100	<hr/> 130

the data recorded and his recollection of the case, it was then decided in what group such cases belonged. No general reaction occurred in any of the patients to whom the dye was administered. In a few cases accidental subcutaneous leakage of the dye was unavoidable, but no local reaction or discomfort followed. Thrombosis after administration of bromsulphalein has not been observed at this hospital.

In table 1, the cases and tests are grouped to give a general idea as to the diseases studied.

In table 2 are shown two groups of tests: (1) those giving readings of 50 per cent or under at five minutes, and zero at thirty minutes, and (2) those giving readings which indicate a retention of dye at both intervals. Thirty-seven tests showed no retention above normal, the average five minute reading being 38, which is close to Rosenthal's average five minute reading of 35. Twenty of these tests were above 35 and sixteen of the twenty above 40. Seventeen were 35 or less. The distribution of these cases with regard to diagnosis will be shown later and perhaps further light thrown on these figures.

Fifty-five tests showed a percentage of dye retention in both samples above the accepted normal. In this table the five minute column gives the amount above the accepted maximum normal of 50. For instance,

TABLE 2—*Tests Showing No Retention Above Normal at Five Minute Reading and Retention Above Normal at Both Five and Thirty Minute Readings*

Number	No Retention Above Normal		Retention Above Normal at Both Intervals		
	Test Number	5 Minute Reading	Test Number	Percentage Over Normal	
				5 Minutes	30 Minutes
1	1	45	5	5	15
2	2	45	7	50+	45
3	11	35	8	5	2
4	12	38	10	40	15
5	13	35	14	5	10
6	15	50	19	28	60
7	16	40	28	20	3
8	17	50	29	40	10
9	20	35	32	10	22
10	22	35	34	35	5
11	23	35	39	40	35
12	24	38	47	35	18
13	25	35	48	50+	85
14	30	45	49	50+	70
15	31	35	54	35	30
16	33	30	55	50+	100
17	35	22	57	10	3
18	36	25	58	5	8
19	40	25	59	5	15
20	41	42	63	10	12
21	44	48	64	40	38
22	45	43	65	20	5
23	50	25	67	22	4
24	51	20	68	50+	70
25	53	30	69	50+	57
26	56	35	70	30	35
27	60	50	71	5	8
28	61	42	73	50+	95
29	72	50	74	50	38
30	81	32	75	38	23
31	89	20	77	30	4
32	93	38	83	2	8
33	128	50	84	35	15
34	129	45	85	50	58
35	135	45	87	35	8
36	136	40	91	50+	100
37	137	45	94	2	Trace
38			96	40	10
39			97	50+	8
40			101	10	3
41			102	50+	60
42			104	10	35
43			105	2	15
44			106	45	8
45			108	45	8
46			109	5	8
47			111	10	2
48			113	50+	50
49			116	50+	100
50			117	50+	100
51			121	35	35
52			125	50+	50+
53			127	10	10
54			131	40	40
55			133	30	30
Total					1,408
Average 5 minute reading, 38					

no. 4 (test 10) gave readings of 90 and 15, and is recorded as 40 above normal at five minutes and 15 above normal at thirty minutes.

It will be noted that fourteen tests show a 50 plus five minute retention above normal or the readings as reported were 100 per cent plus

If the standard maximum concentration is correct, as computed by Rosenthal,<sup>1</sup> i. e., 2 mg of dye per kilogram of body weight representing 4 mg per hundred cubic centimeters of blood at highest concentration, then it would seem impossible to obtain such a reading, for this is the concentration of dye represented in the 100 per cent tube in the set of standards. I have theorized on this point seeking an explanation, but so far have failed. They have all occurred in cases of hepatitis, cholangitis or malignancy—in cases with severe injury of the liver. In one of these cases the same reading was made at thirty minute intervals, though the second concentration was appreciably lighter than the first (about 160 and 120 as estimated). Three times the thirty minute concentration was read 100, once 95, once 85, thence 70, once 60, once 57, once 50, once 45 and once 8 per cent. The last was during the improvement of a patient who suffered from a slight relapse. The patients were usually severely jaundiced, but in the test giving only 8 per cent retention at thirty minutes there was less than 0.8 van den Bergh unit present in the blood removed when the Rosenthal test was performed. Further study of this group of tests showing retention at both intervals has not been made except in connection with their clinical grouping.

Serby and Bloch, already quoted, also reported six cases in which a five minute retention was recorded as 100 per cent plus, five of these being cases of carcinoma of the head of the pancreas, and one a case of sepsis with cloudy swelling of the liver. They offered no explanation of these readings.

Table 3 records the tests in which retention was noted in the thirty minute sample but none above 50 per cent in the five minute sample. It should be noted that only four tests (nos. 3, 10, 12 and 20) showed a five minute reading below 40, three of them being in cases of cirrhosis and the other probably having some injury of the liver. Only four of the twenty cases in this group had no definitely assigned hepatic or gallbladder disease. There is what may be considered a slight sluggishness of the liver in the removal of the bulk of the dye as shown by the first reading, and a definite lag in removal of the dye as shown by the thirty minute retention. This would appear to indicate definite but relatively slight impairment of hepatic function. Only five were below 40 years, and they had either hepatic or some other severe disease.

In table 4 eleven tests are listed in which there was greater than 50 per cent retention at five minutes but no dye remaining in the serum at thirty minutes. Three of these cases had no indications of hepatic or gallbladder disease, and these three cases gave only 52 per cent readings. In this group of cases there appears to be slight retardation in removal of the dye, but the removal is complete in thirty minutes.

TABLE 3—*Tests Showing Retention at Thirty Minutes but Normal at Five Minutes*

No	Age	Test No	Rosenthal		Van den Bergh			Comment
			5 Min	30 Min	Direct	Indirect	Quantitative	
1	54	4	45	10				Chronic hepatitis
2	54	6	45	VFT*				Chronic cholecystitis
3	43	27	35†	10				Cirrhosis, hypertrophic, moderate
4	62	37	50	5				Cirrhosis, hypertrophic, arteriosclerosis
5	43	38	40	5				Cirrhosis, hypertrophic (first test 55 and 10)
6	65	42	48	5				Cirrhosis, hypertrophic and arteriosclerosis (see no 9)
7	50	43	45	7				Syphilis, tertiary, of central nervous system (took 6 doses of arsphenamine after this test)†
8	66	46	50	8				Cholecystitis, chronic, severe jaundice (3 months previous)
9	65	52	42	3				Same case as no 6
10	40	66	38†	5	—	+ —	0.8	Cirrhosis, hypertrophic, early
11	25§	78	48	5	+	+	1.2	Hepatitis, acute (compare nos 14 and 17)
12	35§	79	30†	FT*	—	+ —	0.8	Tonsillitis (possible hepatic hypertrophy)‡
13	50	86	40	10	—	++	1	Pernicious anemia (see no 19)‡
14	25	92	45¶	3	+	+ —	1	Same case as no 11
15	37§	95	45	5				Addison's disease, rephroptosis
16	37§	98	40	8				Hepatitis, acute (previous 100 and 38, 85 and 8, later 0 at 30 minutes)
17	25	100	45¶	3	—	+ —	0.8	Same case as no 11 and 14
18	52	103	42	10	+ —	+	1	Cirrhosis, hypertrophic, adenomatous goiter and arteriosclerosis
19	50	110	40¶	3				Same case as no 13
20	57	112	33†	3				Cirrhosis, hypertrophic, early, arteriosclerosis
21	60	114	50	6				Cirrhosis, hypertrophic, and arteriosclerosis
22	79	122	50	5				Cirrhosis (?), carcinoma of lung (?), senility
23	39§	126	50	12				Cirrhosis, severe, syphilis, tertiary, plastic
24	40	130	50	8				Cirrhosis, severe, syphilis, tertiary, plastic peritonitis, etc (previous 48 and 0, 60 and 10, — and 8, Van den Bergh with first was ++, 1) (five doses of arsphenamine prior to second test)

\* VFT means very faint trace, FT, faint trace

† Indicates a five minute reading below 40

‡ No hepatic disease assigned

§ Under 40 years of age

¶ Repeat tests

TABLE 4—*Cases with Retention Over Fifty at Five Minutes but Normal at Thirty Minutes*

No	Age	Test No	Rosenthal		Comment
			5 Min	30 Min	
1	57	3	65	0	Van den Bergh, negative, acute cholecystitis
2	52	62	55	0	Van den Bergh, 0.8 units, chronic cholelithiasis, mild myocarditis
3	52	80	70	0	Early hypertrophic cirrhosis
4	54	82	52	0	Arteriosclerosis, senility, hernia
5	33	90	52	0	Observation of gastro intestinal disease, not found bad teeth
6	29	115	55	0	Van den Bergh, 1.3 units, cholangitis, acute, catarrhal, moderately severe
7	50	120	52	0	Arteriosclerosis
8	63	123	60	0	Cirrhosis of liver (hypertrophic?), arteriosclerosis, aortitis
9	45	124	60	0	Cholecystitis chronic, moderate, cause undetermined (subicteric)
10	51	134	55	0	Colitis, chronic, atonic, arteriosclerosis
11	40	99	85	0	Van den Bergh, negative, syphilis, tertiary, of central nervous system (liver two fingerbreadths below costal border)

This would appear to indicate a degree of hepatic impairment less than in the foregoing group in table 3. There were only two below 40 years, and one of these had cholangitis.

In table 5, the cases of cholecystitis, acute and chronic, and cholelithiasis are listed, three cases of cholangitis are also shown. In considering these last cases, the question will arise as to whether or not they should be classed as hepatitis. The absence of any marked degree of hepatic tenderness or any appreciable degree of enlargement, and reliance on the clinician's differential ability have seemed to warrant

TABLE 5—Results in Cases of Disease of the Gallbladder and Bile Duct

No	Case No	Age	Rosenthal		Cholecystitis	Comment
			5 Min	30 Min		
1	3	57	65	0	Acute catarrhal, moderate	Van den Bergh negative
2	28	51	85	5	Acute, (and arthritis, hypertrophic)	(Cirrhosis?) third attack
3	18	25	35	0	Subacute, severe	Van den Bergh, — + — early + + +, 51 units)
4	6	54	45	VFT	Chronic (and arrested tuberculosis and myocarditis)	(Stones?), operation stopped
5	21	33	45	0	Chronic (and appendicitis)	Van den Bergh, negative, (pathologic diagnosis gallbladder normal, chronic obliterating appendicitis)
6	25	39	35	0	Chronic	Appendectomy, 1918
7	39	66	50	8	Chronic, with jaundice (stones?)	Liver trouble since 1909, Van den Bergh, 14 and 92 units
8	90	45	60	0	Chronic	Pathologic diagnosis thick wall with severe chronic inflammation
9	94	53	50	0	Chronic (and arterio-sclerosis, moderate, and arthritis)	Hypochlorhydria
10	19	40	35	0	Cholelithiasis	History of syphilis and intense treatment
11	51	52	55	0	Cholelithiasis (and myocarditis, mild)	Van den Bergh, negative, confirmed by operation
Cholangitis						
1	83	29	55	0	Acute, moderately severe	Drank much alcohol from 24 to 48 hours prior to attack, liver slightly enlarged, not tender
2	85	24	100+	100+	Acute, moderately severe	Liver at costal border, moderately tender
3	96	28	90	20	Acute, moderately severe	Liver barely palpable

their separate classification. All three patients were under 30. The second case gave a quantitative van den Bergh reaction of 20 units.

In the three cases of cholecystitis showing some thirty minute retention either hepatic involvement or a stone in the common duct was suspected. The limited number of cases would appear to bear out the observations of other students of this test, namely, that without obstruction of the hepatic bile flow or definite hepatic disease, disease of the gallbladder per se does not cause a retention.

In table 6 twenty-five cases of hepatic cirrhosis are listed, these being subgrouped as atrophic, 1, unclassified, 5, and hypertrophic, 19. In the atrophic case the diagnosis was confirmed at autopsy. In only

eight of these was there more than 10 per cent retention at thirty minutes, and in but six of the remaining cases was there more than 5 per cent

The average five minute reading in the thirty-two tests performed on this group was 61. Only seven cases showed a five minute retention of less than 50, and in two of these there was a higher reading at some other date. There appears, then, to be definite or potential hepatic insufficiency in the elimination of dye in this group, as evidenced by

TABLE 6—*Hepatic Cirrhosis*

No	Case No	Age	Rosenthal		Type	Comment
			5 Min	30 Min		
1	32	55	90	35	Atrophic	Autopsy confirmed, severe abscess of prostate
			90	38		
2	38	50	43	0	Unclassified	Endocarditis, slight (and nephritis?)
3	53	40	33	5	Unclassified	Early, epigastric pain 9 years, ulcer treatment in 1922
4	61	52	70	0	Unclassified	Ulcer could not be confirmed
5	87	36	85	5	Unclassified	History of extensive antisyphilitic treatment in past
6	92	39	50	12	Unclassified	Moderately severe
7	5	39	55	15	Hypertrophic	Jaundice, gallbladder not visualized, tetra chlorophthalein tests positive
8	8	60	55	2	Hypertrophic	Arteriosclerosis, classified as severe
9	13	43	55	10	Hypertrophic	Moderate, possibly syphilitic
			40	5		
10	22	43	35	10	Hypertrophic	Classified as moderate
11	23	56	90	10	Hypertrophic	
12	31	62	50	5	Hypertrophic	Arteriosclerosis
13	35	65	48	5	Hypertrophic	Arteriosclerosis
			42	3		
14	37	40	48	0	Hypertrophic	Plastic peritonitis and syphilis, tertiary (hepatitis?), (classified as severe, treated with arsphenamine between first and second tests)
			60	12		
			—	8		
			50	3		
15	48	54	55	8	Hypertrophic	Anemia after lead poisoning moderate cardiac hypertrophy
16	64	55	83	23	Hypertrophic	Arteriosclerosis, advanced, myocarditis, Van den Bergh negative
17	72	40+	90	10	Hypertrophic	Arteriosclerosis and tonsillitis, Van den Bergh, 1 and 17 units
18	75	52	42	10	Hypertrophic	Adenomatous goiter and arteriosclerosis
19	76	36	60	35	Hypertrophic	Van den Bergh, 1 unit
20	77	55	52	15	Hypertrophic	Syphilis, tertiary and syphilitic cirrhosis severe (autopsied)
21	78	60	95	8	Hypertrophic	Pleurisy and hemorrhoids
22	79	55	60	2	Hypertrophic	Arteriosclerosis and hemorrhoids
23	80	57	33	3	Hypertrophic	Arteriosclerosis and senility, early
24	83	79	50	5	Hypertrophic	Arteriosclerosis
			50	5		
25	89	63	60	0	Hypertrophic	Carcinoma of lung, myocarditis, hydrothorax
						Arteriosclerosis biccup, aortitis

but four cases giving no retention in thirty minutes, as well as by the higher average five minute retention. These are chronic cases, and the great reserve power of the liver as well as its ability to compensate by hypertrophy permits it to function relatively well even with considerable anatomic change. Yet some estimate as to the amount of impairment or degree of compensation may be judged by the retention of the dye, and a check on the hepatic function in cases of cirrhosis may aid in treatment, prognosis or contemplated surgical intervention.

There were three cases in which the diagnosis of syphilitic hepatitis was made or strongly favored, and seven cases apparently due to the

administration of arsphenamine No 6 (case 41, table 7) may be syphilitic instead of arsenical, the primary infection occurred in February, 1928 Only one of the arsenical cases was not also syphilitic Six of the 100 per cent plus readings occurred in this series, all in severe cases and all showing a thirty minute retention above 45 (all but one above 70)

Ten other cases of syphilis occurring in this series are tabulated in table 8 In these cases a diagnosis of syphilis was made or a definite

TABLE 7—*Hepatitis, Syphilitic and Arsenical*

No	Case No	Age	Rosenthal		Van den Bergh			Class	Comment
			5 Min	30 Min	Direct	Indirect	Quantitative		
1	7	65	100+	45	3+	3+	8	Syphilitic	Syphilis, tertiary
			85	18	+ —	+ —	0.9		
2	46	50	35	0	2+	2+	4.4	Syphilitic	Jaundice cleared eight days previously
3	91	33	100+	85				Syphilitic	"Hepatitis, probably syphilitic", syphilis
4	17	20	78	60	4+	4+	12	Arsenical	Under treatment, jaundice on reporting for next dose of arsphenamine, (second Van den Berg two weeks after second Rosenthal)
			35	0	0	+ —	1		
5	40	53	100+	70	3+	3+	15.1	Arsenical	Dermatitis, severe, observation for acute yellow atrophy
			85	30	3+	3+	7.8		
			55	15	2+	2+	2.3		
			55	8	+	+	0.9		
			52	8	+ —	+ —	0.8		
			55	8	—	—	—		
6	41	21	100+	70	3+	3+	18.2	Arsenical	Jaundice seventeen days after fourth dose of arsphenamine, possibly syphilis
7	53	44	100+	95	3+	3+	15	Arsenical	Jaundice three days after second dose, second course, (second test seventeen days after first)
				10	+	+	1.6		
8	84	23	100+	100				Arsenical	Jaundice and vomiting six to eight weeks after last dose of arsphenamine
			80	10					
9	93	24	60	8				Arsenical	Jaundice nine weeks after last dose of arsphenamine of second course
10	47	32	60	3				Arsenical	Not syphilitic, one dose of arsphenamine for pulmonary spirochetosis

history of previous diagnosis and treatment was obtained Fifty per cent of these cases showed retention at thirty minutes, and all but one of these five cases had more than 50 per cent retention at five minutes This case (case 36—no 6, table 8) showed 45 per cent retention at five minutes and 7 per cent at thirty minutes, a definite indication of hepatic impairment The patient was, therefore, not given arsenicals until prepared by a preliminary course of treatment, and consequently no acute hepatitis developed when neoarsphenamine was administered It is believed that here the Rosenthal test was of definite preventive value Only two cases gave less than 40 per cent five minute retention



The three patients giving more than 40 per cent retention in five minutes and none in thirty minutes had received intensive antisyphilitic treatment during the past four to seven months with no evidence of hepatic embarrassment. However, these three patients received iodide and mercury preparation as a routine before the use of arsenicals.

TABLE 8—*Other Syphilitic Cases in Series*

No	Case No	Age	Rosenthal		Comment
			5 Min	30 Min	
1	1	51	45	0	Syphilis, tertiary, of central nervous system
2	2	36	45	0	Syphilis tertiary, of central nervous system (? hepatic symptoms)
3	13	43	55	10	Hypertrophic cirrhosis, probably syphilis of central nervous system
4	19	40	35	0	Cholelithiasis, history of syphilis and treatment
5	30	52	25	0	Syphilis, tertiary, of central nervous system
6	36	50	45	7	Syphilis, tertiary, (took six doses of arsphenamine later following succinamide)
7	37	40	48	0	Syphilis, tertiary, hypertrophic cirrhosis, (? hepatitis), (received arsphenamine between first and second tests)
			60	12	
			50	8	
			50	3	
8	50	44	42	0	Syphilis, tertiary (gummatous change in lung)
9	76	36	60	35	Syphilis, tertiary, and syphilitic cirrhosis, severe, (autopsied)
10	87	36	85	5	Cirrhosis, unclassified, history of extensive antisyphilitic treatment in past

TABLE 9—*Hepatitis, Nonsyphilitic and Nonarsenical*

No	Case No	Age	Rosenthal		Van den Bergh			Diagnosis	Comment
			5 Min	30 Min	Direct	Indirect	Quantitative		
1	4	54	45	10				Chronic hepatitis, arthritis	Wassermann reaction negative
2	15	38	10	0				Subacute, nephrolithiasis and peritonitis	No autopsy, Wassermann and Kahn reactions negative
			70	3					
3	45	30	100+	100	4+	4+	31.5	Acute hepatitis, severe, cause undetermined	Some tooth trouble
			72	4	2+	2+	4.6		
			80	4	2+	2+	3.5		
			100+	8	+	+	0.8		
			95	8	+	+	0.9		
4	52	25	70	5	+	+	2.4	Acute (Van den Bergh 18 days before first Rosenthal 62 units)	Heavy drinking prior to attack
			48	5	+	+	1.2		
			45	3	+ —	+ —	1		
			45	3	—	—			
5	59	36	100	38	2+	2+	3.8	Acute hepatitis, (arsenical ?), (not syphilitic, Wassermann reaction negative)	Two doses of arsphenamine 10 days previously
			85	8	+	+	1		
			40	8	+ —	+ —			
			—	0	—	+ —			

The five patients with nonsyphilitic or nonarsenical hepatitis showed definite retention at some stage of the disease (table 9). None of the five minute readings were less than 40 per cent. One of these cases should probably be classed as arsenical (no 5—case 59) as the patient admitted late in the illness that he “unofficially” received two injections of neoarsphenamine, but strongly denied syphilitic infection. No evidence of syphilis was found, and the Wassermann reaction of the blood was negative.

The seven cases of malignancy in which this test was applied showed a definite retention (table 10) All but two diagnoses were confirmed by operative or autopsy observations Both of these showed definite hepatic enlargement Several other writers have stressed the value of this test for determining hepatic metastases in cases showing no jaundice As a guide to treatment, especially with regard to surgical intervention, the test is of much value

Forty cases are listed in table 11 as clinically nonhepatic, that is, there was no clinical evidence to indicate hepatic involvement In table 11 two cases (nos 39 and 40, or cases 74 and 82) are included which were diagnosed hypertrophic cirrhosis As noted, the diagnosis in these two cases was influenced by the Rosenthal test Four other cases showed

TABLE 10—*Malignancy*

No	Case No	Age	Rosenthal		Van den Bergh			Diagnosis	Comment
			5 Min	30 Min	Direct	Indirect	Quantitative		
1	26	62	60	22	2+	2+	83	Generalized abdominal carcinoma	Confirmed by operation, no autopsy
2	54	37	100+	70	3+	3+	171	Observation malignancy (pancreas?)	Liver 1 inch above umbilicus
			100	58	3+	3+	16		
			100+	60	4+	4+	231		
3	55	53	100+	57				Carcinoma of liver, pancreas and stomach	Gastric distress for 20 years, no autopsy
4	56	46	80	35	2+	2+	89	Lymphosarcoma, retroperitoneal and mesenteric	Limited hepatic involvement but obstruction
5	68	42	100+	100				Generalized abdominal carcinoma	Confirmed by operation, no autopsy
6	81	37	100+	50				Melanosarcoma, generalized	Massive hepatic metastasis, autopsy
7	88	79	50	5				Carcinoma of lung (?), cirrhosis of liver (?)	Hydrothorax, right

more than a trace of retention at thirty minutes No 31 (case 9) probably had at least a congested liver In no 32 (case 36) the patient had syphilis, and it may be assumed that there was otherwise undiscovered hepatic injury In no 34 (case 65) the condition was diagnosed pernicious anemia, and the patient gave a history of dysentery in the Philippines in 1898, with a later history of watery stools with some blood for the past few years One month prior to admission he had been jaundiced In this case there were two possibilities either that he had injury to the liver from intestinal infection and toxemia, or that there was some change in hepatic function in such a severe disease of the blood as pernicious anemia No 36 (case 71) cannot be explained, there is some question as to whether this is actually a case of Addison's disease

The average five minute reading for this entire group was 42.07 per cent If the seven readings in the six cases which also showed more than a trace of dye in thirty minutes are omitted, the average five

minute reading for the remaining thirty-four cases becomes 39.85 per cent—approximately 40 per cent

If these thirty-four cases are subdivided into two groups, one to include all cases with a five minute retention greater than 40 per cent

TABLE 11—*Nonhepatic Cases*

No	Case No	Age	Rosenthal		Diagnosis	Comment
			5 min	30 Min		
1	1	51	45	0	Syphilis, tertiary, of central nervous system	
2	2	36	45	0	Syphilis, tertiary of central nervous system	(? of hepatic symptoms)
3	10	41	35	0	Constipation, chronic, severe	
4	11	63	38	0	Arteriosclerosis, myocarditis	
5	12	54	35	0	Diabetes mellitus, severe	
6	14	60	50	0	Arteriosclerosis	
7	16	55	50	0	Multiple neuritis, sequelae	
8	20	38	45	0	Spastic colitis	
9	27	29	30	0	Chronic nephritis	
10	29	50	22	0	Myocarditis and hypertension	
11	30	52	25	0	Syphilis, tertiary, of central nervous system	
12	33	31	25	0	Appendicitis, chronic	Pathologic diagnosis acute exacerbation
13	34	?	42	0	Enterocolitis, chronic, recurrent	
14	42	38	25	0	Varicose veins and ureteral kink	Cholecystectomy, 1925
15	43	15	20	0	Stomatitis	Slight gastric symptoms
16	44	34	30	0	Gastritis, chronic	Probably alcoholic
17	49	39	50	0	Gastritis, chronic	
18	50	44	42	0	Syphilis, tertiary	Pulmonary gumma
19	57	47	50	0	Duodenal ulcer and chronic appendicitis	Confirmed by operation
20	62	34	32	0	Neurasthenia	
21	66	30	20	0	Gastric neurosis and tonsillitis	
22	67	33	52	0	Observation, gastro intestinal disease not found	Bad teeth
23	69	42	38	0	Myelogenous leukemia	
24	86	50	52	0	Arteriosclerosis	
25	95	40	45	0	Arteriosclerosis, constipation	
26	93	36	45	0	Alcoholism, chronic, severe	
27	99	56	40	0	Duodenal ulcer, chronic	
28	63	54	52	0	Arteriosclerosis, senility, hernia	
29	97	51	55	0	Colitis, chronic, atonic and arteriosclerosis	
30	100	46	45	0	Arteriosclerosis, eczema	Disease of gallbladder not found
31	9	35	90	15	Valvular heart disease (mitral regurgitation and stenosis, auricular fibrillation)	Probable congested liver
32	36	50	45	7	Syphilis tertiary, of central nervous system	Took six shots of arsphenamine later, following succinamide
33	60	35	30	FT	Tonsillitis	"Possible hepatic hypertrophy"
34	65	50	40	10	Pernicious anemia	Jaundice, history of dysentery, 1898
35	70	78	52	Trace	Cardiac hypertrophy and arteriosclerosis	Congestion?
36	71	37	45	5	Addison's disease and nephropathy	
37	73	40	85	0	Syphilis, tertiary, of central nervous system	
38	21	47	38	0	Arteriosclerosis, general, moderate	
39	74	47	60	3	Hypertrophic cirrhosis, arteriosclerosis, myocarditis	Diagnosis influenced by Rosenthal test
40	82	47	50	6	Hypertrophic cirrhosis, arteriosclerosis	Diagnosis influenced by Rosenthal test, liver not enlarged

which have a diagnosis warranting a suggestion of hepatic involvement, and the other group including the remainder, rather interesting and perhaps instructive figures are obtained

In table 12 are tabulated the first subgroup of nonhepatic cases. The diagnoses in these cases are considered sufficient to warrant at

least a suggestion of hepatic involvement The average five minute retention of this group was 49.4 per cent

In the second subgroup of nonhepatic cases, all but two of the five minute readings were below 40 per cent (table 13) The diagnoses,

TABLE 12—Nonhepatic Cases with More than 40 Per Cent Five Minute Retention (with Diagnosis Permitting Suggestion of Hepatic Involvement) \*

Case No	No	Rosenthal		Diagnosis
		5 Min	30 Min	
1	1	45	0	Syphilis, tertiary, of central nervous system
2	2	45	0	Syphilis, tertiary, of central nervous system
6	14	50	0	Arteriosclerosis
8	20	45	0	Spastic colitis
13	34	42	0	Enterocolitis, chronic, recurrent
17	49	50	0	Gastritis, chronic
18	50	42	0	Syphilis, tertiary
19	57	50	0	Duodenal ulcer and chronic appendicitis
24	86	52	0	Arteriosclerosis
25	95	45	0	Arteriosclerosis, constipation
26	98	45	0	Alcoholism, chronic, severe
27	99	40	0	Duodenal ulcer, chronic
28	63	52	0	Arteriosclerosis, senility, hernia
29	97	55	0	Colitis, chronic, atonic and arteriosclerosis
30	100	45	0	Arteriosclerosis, eczema (disease of gallbladder not found)
35	70	52	Trace	Cardiac hypertrophy and arteriosclerosis
37	73	85	0	Syphilis, tertiary, of central nervous system
Totals	17	840		
Average		49.4		

\* Of the cases listed in table 11, nos 5, 31, 32, 34, 36, 39 and 40 are omitted as cases with probable hepatic involvement

TABLE 13—Nonhepatic Cases with Less than 40 Per Cent Five Minute Retention (Except for Two Above Fifty Who Showed no Condition Permitting Suggestion of Hepatic Involvement)

Case No	No	Rosenthal		Diagnosis
		5 Min	30 Min	
3	10	35	0	Constipation, chronic, severe
4	11	38	0	Arteriosclerosis, myocarditis
5	12	35	0	Diabetes mellitus, severe
7	16	50	0	Multiple sclerosis, sequelae of
9	27	30	0	Chronic nephritis
10	29	22	0	Myocarditis and hypertension
11	30	25	0	Syphilis, tertiary, of central nervous system
12	33	25	0	Appendicitis, chronic
14	42	25	0	Varicose veins and ureteral link (cholecystectomy, 1925)
15	43	20	0	Stomatitis
16	44	30	0	Gastritis, chronic (probably alcoholic)
20	62	32	0	Neurasthenia
21	66	20	0	Gastric neurosis and tonsillitis
22	67	52	0	Observation, gastro intestinal disease not found (bad teeth)
23	69	38	0	Myelogenous leukemia
33	60	30	FT	Tonsillitis, "possible hepatic hypertrophy"
38	21	38	0	Arteriosclerosis, general, moderate
Totals	17	545		
Average		32		

histories and physical observations in these two cases were not considered definite enough to permit placing them in table 12 The average five minute retention of this group of seventeen cases was 32 per cent

In these last two tables a feature is demonstrated which had repeatedly impressed me while studying the series of cases, namely, that a five

minute retention between 40 and 50 per cent should create a suggestion of hepatic involvement. As these five minute retentions above 40 per cent occur frequently in cases showing no retention at the thirty minute period, it is my belief that the five minute sample should always be obtained, if possible.

#### SUMMARY

1 One hundred and thirty Rosenthal bromsulphalein tests in 100 cases are reported. No unfavorable reactions or results have been observed.

2 Thirty-seven tests showed no retention above Rosenthal's normal figures. The average five minute reading for this group was 38 per cent.

3 Fifty-five tests showed a retention above normal in both samples.

4 Fourteen five minute samples are recorded above 100 per cent. This is unexplained, but bilirubinemia seems to be a causative factor.

5 Of twenty-four tests showing a thirty minute retention and 50 per cent or less at five minutes, only four fell below 40 per cent at five minutes.

6 Eleven cases showed greater than 50 per cent at five minutes and no retention at thirty minutes. All but three had some hepatic or gallbladder disease.

7 Cases of disease of the gallbladder and bile duct gave no retention except when there was hepatic involvement, definite or suspected.

8 Of twenty-five cases of hepatic cirrhosis, 44 per cent (eleven cases) showed 5 per cent or less retention at thirty minutes, the average five minute reading of this group (thirty-two tests) was 61 per cent. Only five cases showed less than 50 per cent retention at five minutes (two others did but had other higher retentions). Only four cases showed no thirty minute retention.

9 All of the seven cases of arsenical hepatitis showed retention. Two of three cases of syphilitic hepatitis showed retention, the third case had been free from jaundice for eight days preceding the Rosenthal test. One case of the arsenical group showed permanent injury by the Rosenthal test after the van den Beigh reaction had become negative.

10 Five of ten other patients in the series who had syphilis, but no diagnosis of hepatic involvement, showed retention. In cases of syphilis with suspected hepatic involvement the control of arsenical treatment by this test is indicated.

11 All but one of fifteen cases of hepatitis showed definite retention. The one exception was not tested until eight days after jaundice had disappeared (tables 7 and 9).

12 The observations of others in malignant disease of the liver are confirmed

13 Forty cases (40 per cent of the series) were not considered clinically as evidencing hepatic involvement. Two of these were diagnosed cirrhosis of the liver, but the diagnosis was influenced by the Rosenthal test. In three of the four other cases showing more than a trace of dye retention at thirty minutes hepatic dysfunction could reasonably be assumed. Omitting these six cases, the average for the remainder of the group was 40 per cent retention at five minutes.

#### CONCLUSIONS

1 The bromsulphalein dye, used as directed by Rosenthal, is of distinct value in determining the presence and degree of hepatic dysfunction.

2 Bromsulphalein is safer, less toxic, less irritating and easier to use than phenoltetrachlorophthalein.

3 From 35 to 38 per cent may be considered as the normal average five minute retention.

4 Between 40 and 50 per cent retention at five minutes should create suspicion of hepatic disorder. Other criteria need to be used in such a case.

5 Above 50 per cent retention at five minutes is strongly suggestive of hepatic disease or disorder, and combined with a thirty minute retention is almost diagnostic of injury to the liver.

6 The test is of special value (1) in determining functional or anatomic damage to the liver in cases of disease of the gallbladder or bile duct, (2) in determining hepatic involvement in cases of malignancy, (3) in controlling antisyphilitic arsenical treatment, (4) in determining the degree of residual disorder after acute disease of the liver, (5) in determining hepatic involvement in cases of tertiary syphilis and (6) in confirming suspected disease of the liver without jaundice.

7 The five minute sample is of such frequent value that it should be collected as a routine.

8 This test is a valuable addition to the means of study of hepatic disease, but it should not be allowed to replace thorough clinical observation nor should it be used independently of other tests if they are indicated.

## CALCIUM STUDIES

### VI THE EFFECT OF PARATHYROID EXTRACT ON THE DIFFUSIBILITY OF CALCIUM IN HUMAN BEINGS \*

A CANTAROW, M D

PHILADELPHIA

A decreased total serum calcium is a constant observation in parathyroprivic tetany, but there is considerable difference of opinion in the literature as to the distribution of the diffusible and nondiffusible fractions in this condition. The divergent results obtained may be explained in part by the fact that different experimental methods have been used by different investigators. For reasons which have been stated previously <sup>1</sup> it seems that, from a physiologic point of view, the consideration of the cerebrospinal fluid as the diffusible portion of the serum calcium is more satisfactory than the determination of diffusible calcium by ultrafiltration or dialysis.

Cameron and Moorhouse <sup>2</sup> found that in parathyroidectomized dogs the total serum calcium was greatly diminished but that the spinal fluid calcium was little altered. They concluded that in parathyroprivic tetany the reduction is in the nondiffusible calcium. The same conclusion was reached by Cruickshank <sup>3</sup>. On the other hand, Moritz <sup>4</sup> and von Meysenbug and McCann <sup>5</sup> noted a reduction in both diffusible and nondiffusible calcium in the same ratio. Moritz <sup>6</sup> found that following the injection of parathyroid extract in rabbits, there was an increase in both diffusible and nondiffusible calcium, the increase being more marked

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\* From the Medical Service of Dr Thomas McCrae and the Department for Diseases of the Chest, Jefferson Hospital

1 Cantarow, A. Calcium Studies. V. The Relationship Between the Calcium Content of Cerebrospinal Fluid and Blood Serum in Health and in Disease, *Arch Int Med* **44** 670 (Nov) 1929

2 Cameron, A. T., and Moorhouse, V. H. K. Tetany of Parathyroid Deficiency and the Calcium of the Blood and Cerebrospinal Fluid, *J Biol Chem* **63** 687, 1925

3 Cruickshank, E. W. H. Studies on Experimental Tetany, *Biochem J* **17** 13, 1923

4 Moritz, A. R. The Effect of Ultra-Violet Radiation on the State of Serum Calcium, *J Biol Chem* **64** 81, 1925

5 Von Meysenbug, L., and McCann, G. F. The Diffusible Calcium of the Blood Serum. 2. Human Rickets and Experimental Tetany, *J Biol Chem* **47** 541, 1921

6 Moritz, A. R. The State of the Serum Calcium in Experimental Hypo- and Hyper-Calcaemia, *J Biol Chem* **66** 343, 1925

in the diffusible fraction Liu<sup>7</sup> injected parathyroid extract into two patients with parathyroid tetany and found that the total serum calcium rose, the rise being greater in the diffusible than in the nondiffusible portion

In the present investigation simultaneous determinations of the blood serum and cerebrospinal fluid calcium in eleven patients were made, before and at four hour intervals after the intramuscular injection of 40 units of parathyroid extract<sup>8</sup> The patients included four with essential epilepsy, two with mental deficiency, two imbeciles and three with bronchial asthma The location of the patients necessitated the lapse of thirty-six hours between the collection of the material and the calcium determinations Numerous checks on serum and spinal fluid, which was allowed to stand at room temperature for forty-eight hours showed no change in calcium content beyond the experimental

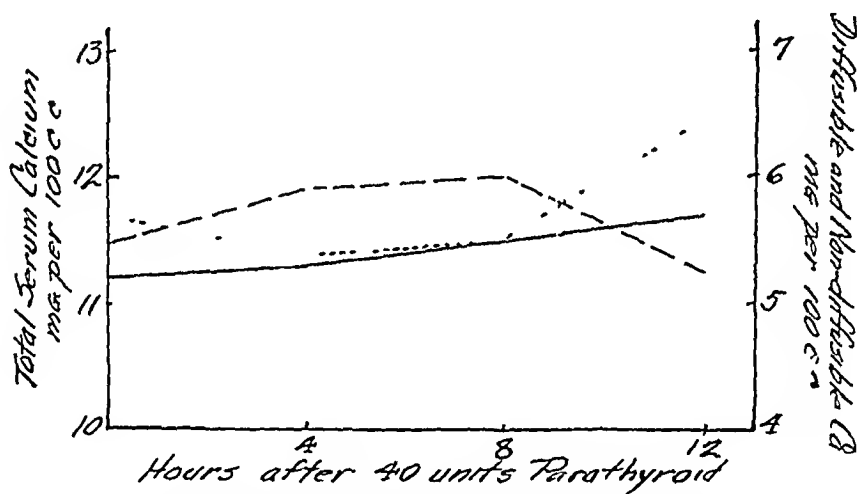


Chart 1 (case 1) —Calcium determinations in a patient with epilepsy In this and the following charts, the relationship between the total blood serum calcium and its diffusible and nondiffusible fractions before and at four hour intervals after the intramuscular administration of 40 units of parathyroid extract are shown The total calcium is represented by the solid line, the diffusible calcium by the broken line and the nondiffusible calcium by the dotted line

error of 2 per cent The method used for the calcium determinations was the Clark-Collip modification of the Kramer-Tisdall method for determining serum calcium<sup>9</sup>

7 Liu, S H The Partition of Serum Calcium into Diffusible and Nondiffusible Portions, *Chinese J Physiol* **1** 331, 1927

8 The preparation used was parathyroid extract-Collip, supplied by Eli Lilly and Company, through the courtesy of Dr J H Warvel

9 Clark, E P, and Collip, J B A Study of the Tisdall Method for the Determination of Blood Calcium with a Suggested Modification, *J Biol Chem* **63** 461, 1925



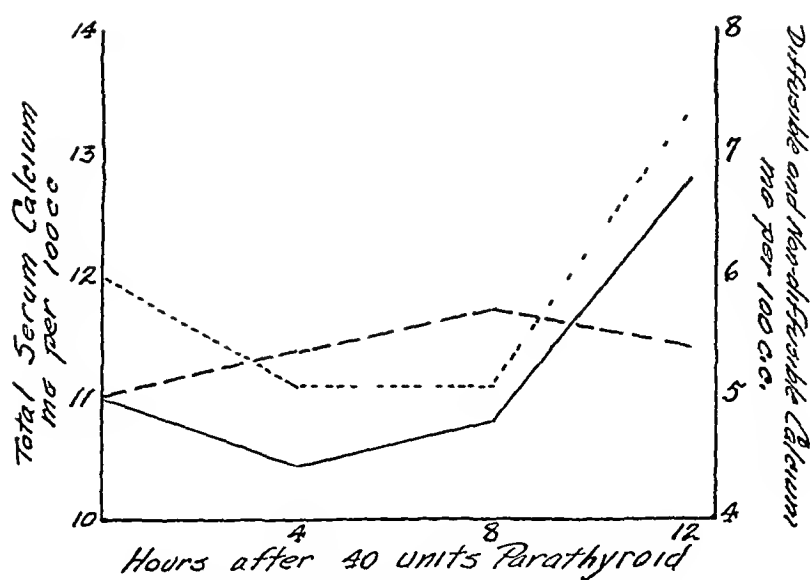


Chart 2 (case 2) —Calcium determinations in a patient with epilepsy

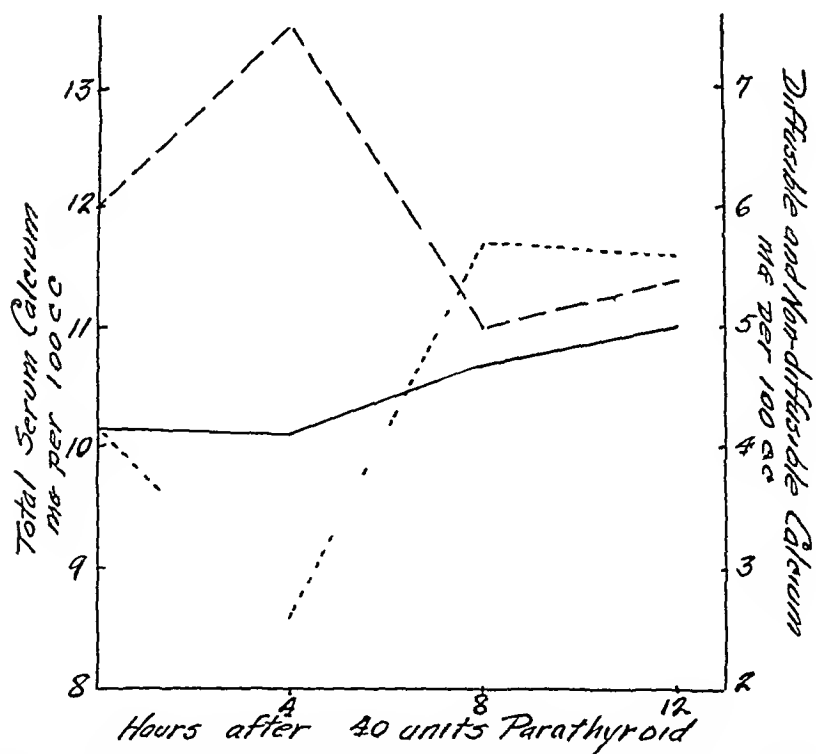


Chart 3 (case 3) —Calcium determinations in a patient with epilepsy

## EXPERIMENTAL DATA

The results obtained are shown in the accompanying charts. The term "diffusible" is applied to the cerebrospinal fluid calcium, the difference between it and the total serum calcium being considered non-diffusible.

*Total Serum Calcium*—The serum calcium before the injection of parathyroid extract was from 7 to 11.5 mg per hundred cubic centimeters, the figures for the three patients with asthma being 7, 7.5 and 8.5 mg. One patient with epilepsy had a serum calcium of 11.2 mg, and one with imbecility, 11.5 mg, the other figures were within the normal limits of from 9 to 11 mg. As was noted in previous studies,<sup>10</sup> there was a general tendency toward an increase in serum calcium, the most marked rise occurring from eight to twelve hours after the injection in most instances. In cases 1, 3 and 5, the increase was comparatively slight. However, as Hunter and Aub<sup>11</sup> have pointed out, alterations in calcium metabolism may follow the administration of the parathyroid hormone without any significant change in the level of serum calcium. In the patients with bronchial asthma a marked elevation occurred, amounting to 5.2 mg in case 2.

*Cerebrospinal Fluid Calcium*—The control values ranged from 4.9 to 6 mg. The normal cerebrospinal fluid calcium was found in a previous study<sup>1</sup> to be from 4.5 to 5.5 mg per hundred cubic centimeters. In this group of patients five showed figures above normal: case 3, epilepsy, 6 mg; case 5, imbecility, 5.8 mg; case 8, mental deficiency, 5.6 mg; cases 10 and 11, bronchial asthma 6 mg and 5.7 mg, respectively. Following the injection of parathyroid extract, the general trend was toward a rise in the spinal fluid calcium. In only two instances (cases 6 and 7) did this figure fail to rise above the high limit of normal. In only two patients, however, was the elevation marked (cases 3 and 5), and it appears significant that in case 3 an increase of 1.5 mg at the end of four hours was accompanied by a slight decrease in the total serum calcium. Another observation worthy of attention is that in two of the patients with bronchial asthma (cases 10 and 11) there was a preliminary fall in cerebrospinal fluid calcium at the end of four hours, coincident with a definite rise in total serum calcium.

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10 Cantarow, A., Caven, W. R., and Gordon, B. L. Changes in the Chemical and Physical Characteristics of the Blood Following the Administration of Parathyroid Hormone, *Arch. Int. Med.* **38**: 509 (Oct.) 1926. Cantarow, A., Dodek, S. M., and Gordon, B. L. Calcium Studies in Jaundice, *Arch. Int. Med.* **40**: 129 (Aug.) 1927.

11 Hunter, D. and Aub, J. C. Lead Studies. 15 The Effect of Parathyroid Hormone upon the Excretion of Lead and of Calcium in Patients Suffering from Lead Poisoning. *Quart. J. Med.* **20**: 136, 1927.

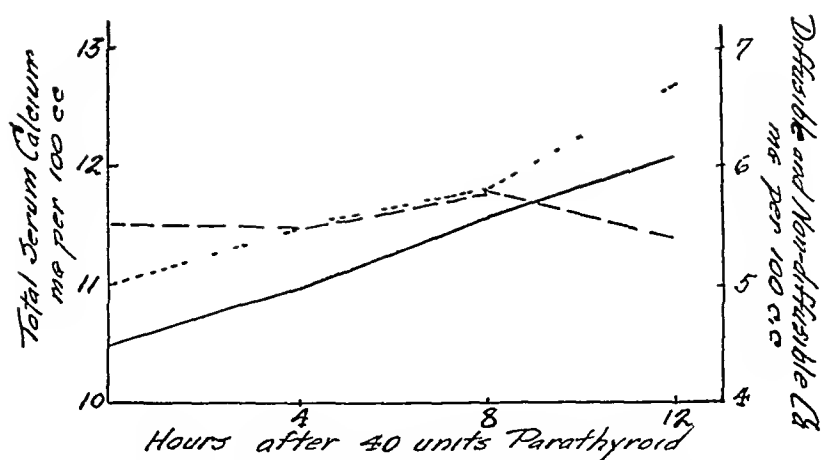


Chart 4 (case 4) —Calcium Determinations in a patient with epilepsy

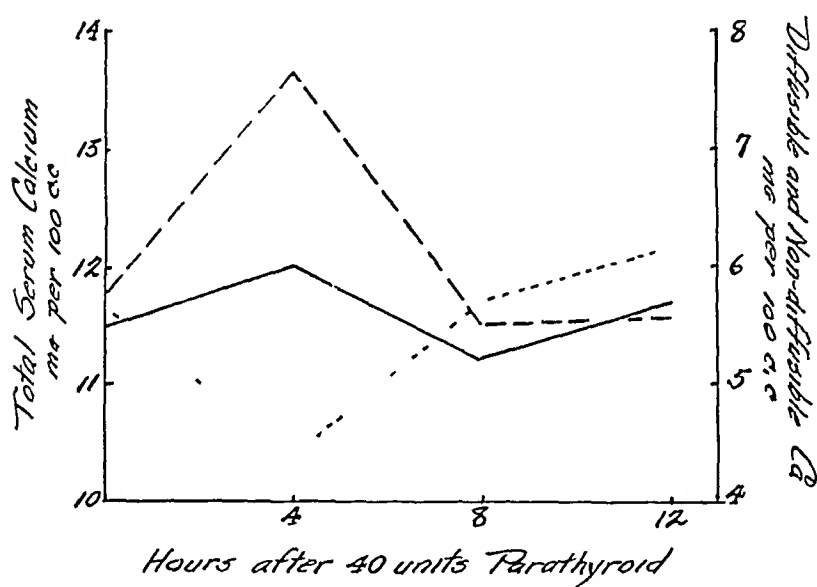


Chart 5 (case 5) —Calcium determinations in an imbecile

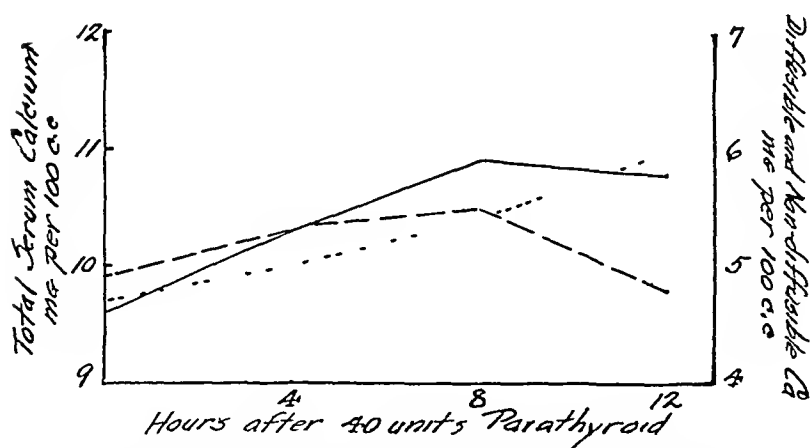


Chart 6 (case 6) —Calcium determinations in an imbecile

*Nondiffusible Calcium*—The normal values for nondiffusible calcium in a previous series were from 4.7 to 5.75 mg per hundred cubic centimeters<sup>1</sup> In the present series five were within normal limits, one (case 2, epilepsy) was above normal (6 mg), and five were below normal (case 3, epilepsy, 4.15 mg, case 7, mental deficiency, 3.95 mg, cases 9, 10 and 11, bronchial asthma, 1.8, 1.5, 2.8 mg, respectively)

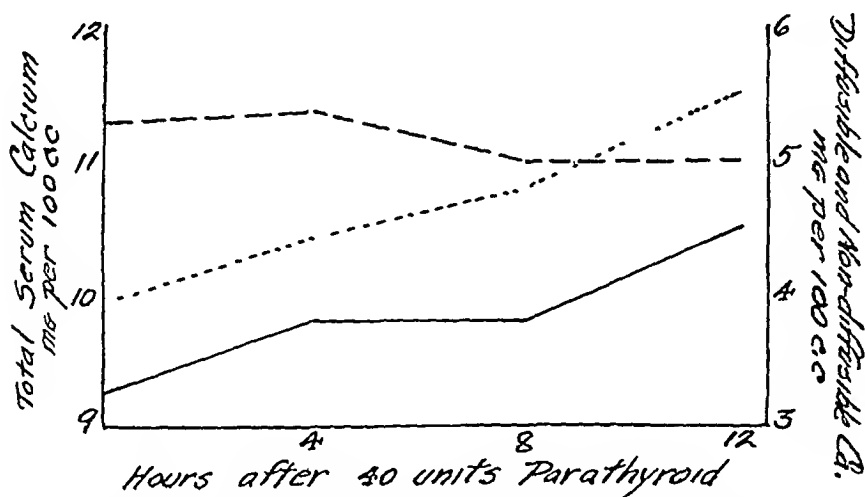


Chart 7 (case 7) —Calcium determinations in a mentally deficient patient

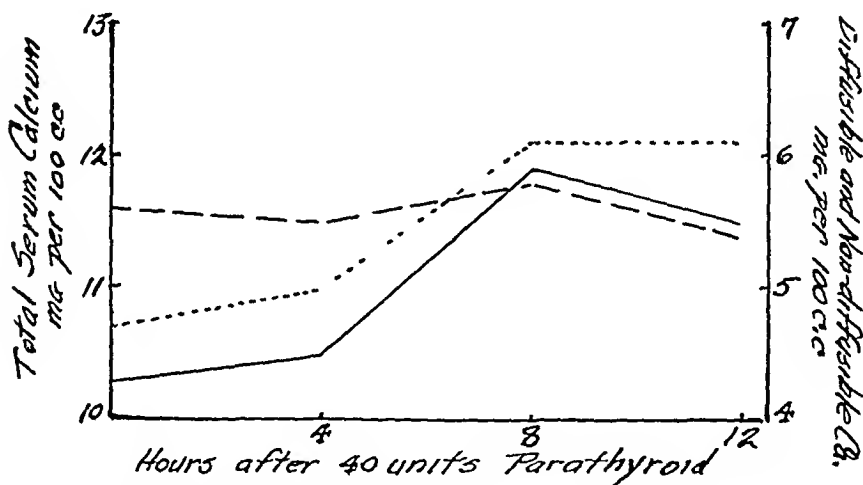


Chart 8 (case 8) —Calcium determinations in a mentally deficient patient

After the injection of parathyroid extract, there was a distinct elevation of nondiffusible calcium in every case. The greatest rise was found at the end of the twelve hour period in all but one patient (case 10). This patient was the only one in whom the nondiffusible calcium did not exceed the diffusible at the end of twelve hours, although prior to the injection the reverse was the case in all but two instances (cases 1 and 2).

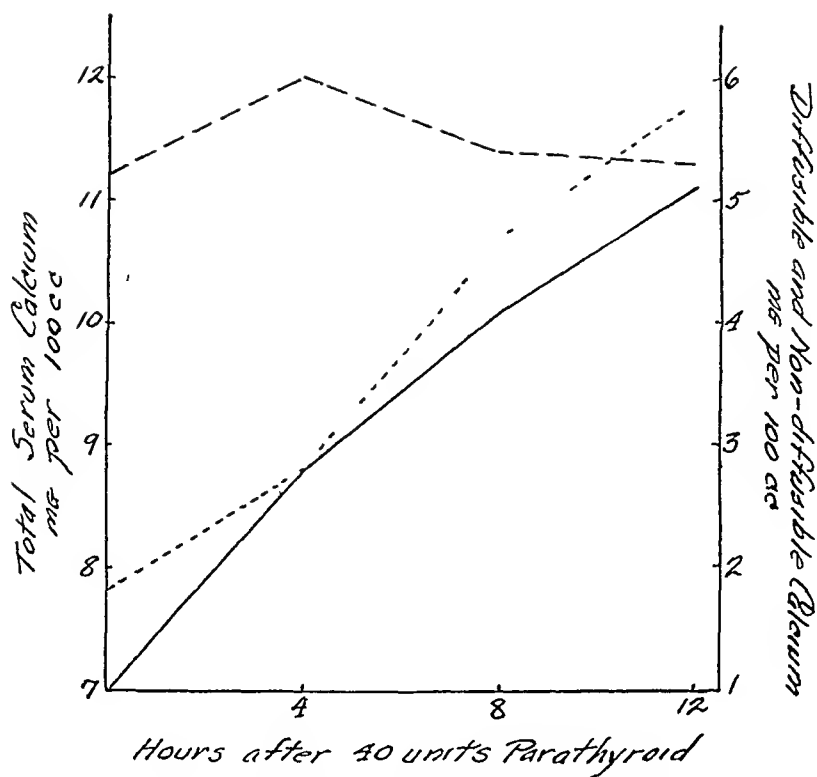


Chart 9 (case 9) —Calcium determinations in a patient with bronchial asthma

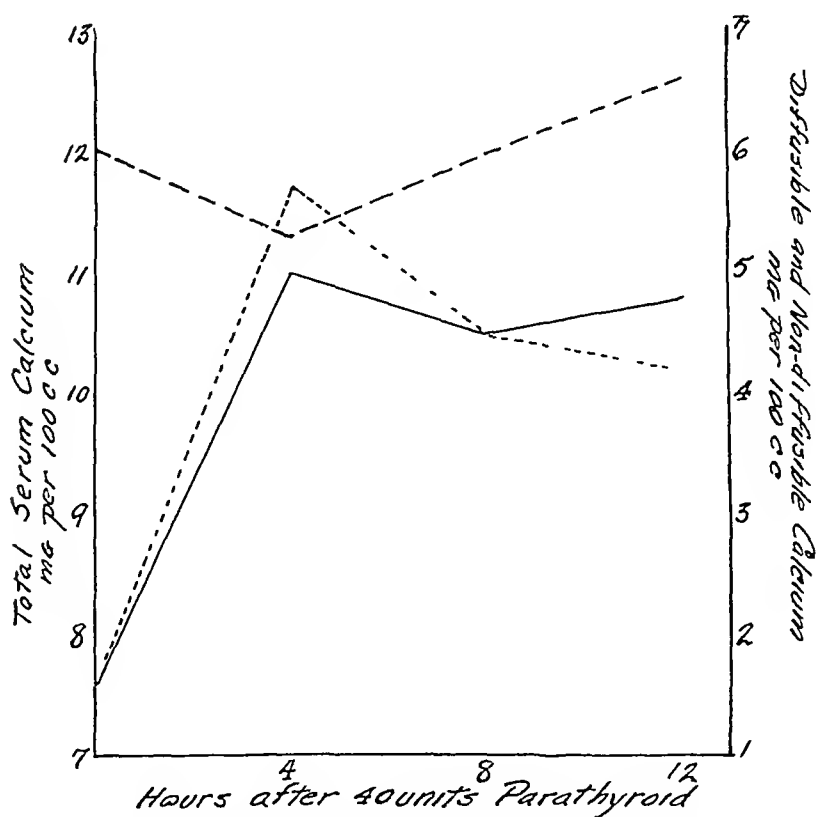


Chart 10 (case 10) —Calcium determinations in a patient with bronchial asthma.

*Ratio of Diffusible to Nondiffusible Calcium*—The change that follows the administration of parathyroid extract may be shown by a consideration of the ratio of diffusible to nondiffusible calcium as illustrated in the accompanying table. In five cases there was an increase in the ratio at the end of four hours, but at the end of the twelve hour period the figure was below the control in every patient, the lowest figure in every case but one (case 10) being obtained at this time.

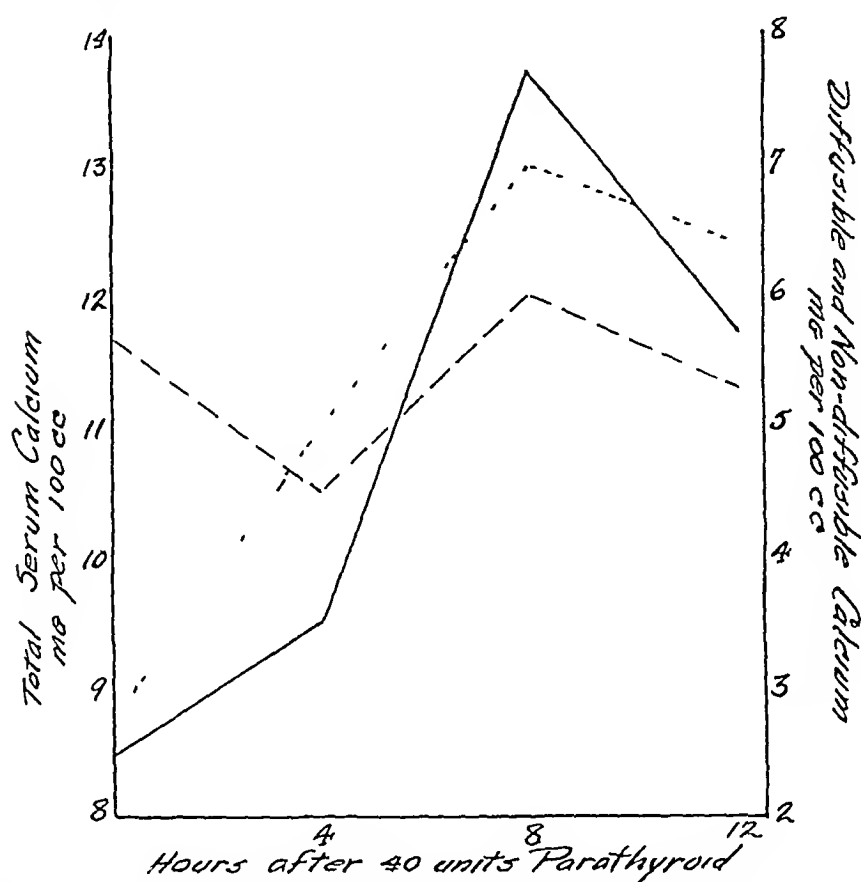


Chart 11 (case 11) —Calcium determinations in a patient with bronchial asthma

*The Ratio of Diffusible to Nondiffusible Calcium Before and at Four Hour Intervals After the Intramuscular Injection of 40 Units of Parathyroid Extract*

Cases	Control*	4 Hours*	8 Hours*	12 Hours*
1	98	109	109	81
2	83	105	111	73
3	144	288	87	96
4	110	100	100	81
5	101	175	96	91
6	104	106	101	80
7	134	120	104	91
8	119	110	95	88
9	288	214	115	91
10	400	93	183	157
11	203	90	86	82

\* Ratios expressed as percentages

## COMMENT

Parathyroid extract appears to affect both the diffusible and the nondiffusible fractions of serum calcium. In this respect, the observations in the present study confirm those of Moritz.<sup>6</sup> He believed, however, that the diffusible calcium was affected more than the nondiffusible, whereas the figures in the present study seem to indicate that the reverse is the case. This apparent contradiction may be due, as previously suggested, to the difference in experimental method. Furthermore, the work of Moritz was done on rabbits, a species which appears to be much less responsive to parathyroid extract than other animals. It would seem that a more exact index of the calcium distribution in the tissues is obtained by the simultaneous determination of blood serum and cerebrospinal fluid calcium, which takes into account the variable factor of cell membrane permeability. This factor is disregarded in dialysis and ultrafiltration experiments, a fact which may be of particular importance in view of the decided effect of calcium on cell permeability.

The most marked increase in nondiffusible calcium occurred in patients in whom this factor was originally low, as in those with bronchial asthma. That the diffusible and nondiffusible values may vary independently is evidenced by the fact that at times both increased simultaneously (cases 6, 9 and 11), and at times an increase in one was accompanied by a decrease in the other. That the level of diffusible calcium is not entirely dependent on the total serum calcium is shown in cases 2, 3 and 10, in which the former factor increased coincidentally with a diminution in the latter. The same point is illustrated strikingly in cases 9, 10 and 11, and to a lesser degree in other instances, in which the reverse condition prevailed, namely, a decrease in diffusible calcium coincidentally with an increase in total serum calcium.

It appears, therefore, that the parathyroid hormone, in some cases showing a normal calcium distribution, causes a preliminary increase in the ratio of diffusible to nondiffusible calcium, followed by a more marked and more prolonged decrease in this ratio. In other instances, particularly those with a low nondiffusible fraction, the ratio decreases steadily over the twelve hour period. Variations in this ratio bear no constant relation to the total serum calcium.

# THE SYSTOLIC BLOOD PRESSURE IN DUODENAL AND IN GASTRIC ULCER

A STATISTICAL STUDY \*

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AND

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This study was undertaken with the hope of determining whether or not patients suffering from duodenal or gastric ulcer have low systolic blood pressures. The data were compiled from the records of patients with duodenal or gastric ulcer examined in the Mayo Clinic by a diversified but well trained group of internists. Thus, multiple personal equations are expressed in the readings of blood pressure. No reading was taken with the subject under consideration in mind. The readings were impersonally recorded, by the auscultatory method, usually with the patient in the sitting position, using a spring sphygmomanometer. These instruments are corrected for variations against a mercury sphygmomanometer every seven days, so that it would be impossible to have a gross mechanical error in reading. The readings were recorded immediately on a history sheet, and from these records the charts were compiled and curves constructed. This work was done by a statistician who had no knowledge of the preconceived hypothesis. The compilation and mathematics of biometry were checked throughout by other statisticians. We are therefore able to transcribe the results in charts, curves and explanations for a matter of record.

The first series of cases studied comprised 865 of duodenal ulcer and 561 of gastric ulcer. In selecting the patients, the question of whether blood pressure was normal or abnormal was not considered. The series included cases of severe hypertension, due to independent conditions associated only by coincidence.

The data were corrected for age and weight against 1,016 cases encountered in the routine of work at the clinic, in some of which the general examination gave negative results, cases of ulcer and of carcinoma of the stomach were excluded from this group. The patients in this group, which was used as a control, were not all normal, but cases of hypotension as well as of hypertension were included and the weight distribution (thin normal and stout) seemed fairly regular.

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<sup>1</sup> From the Division of Medicine, the Mayo Clinic.



In making the corrections for age and weight the cases were divided into age groups, and each group was subdivided, according to weight, into three classes called, respectively, "thin," "normal" and "stout" In making up the classes according to weight, consideration was given to age and height as well as to weight A chart of normal weight was employed as a standard in this part of the work of classification In order to obtain a so-called normal group, cases were considered to be normal in which the data were 5 per cent above or 5 per cent below the normal as established on the standard chart The control cases were similarly grouped and classified In the control cases, the mean blood pressures were calculated for the patients in each of the three weight groups Then the results in the various age groups and weight classes in the cases of ulcer were corrected against the values established for the groups and classes in the control group As shown in the following problem, the mean blood pressure ( $n$ ,  $o$  or  $p$ ) was calculated in each age group and in each of the three weight classes The result, in each instance, was multiplied by the frequency ( $a$ ,  $b$  or  $c$ , that is, the number of patients in the group) in the corresponding weight class of the group of patients with ulcer The sum of these products was divided by the sum of the frequencies in the group with ulcer ( $d$ ), and the quotient was an average ( $r$ ) which represented the mean blood pressure in the control cases if they had been distributed as the cases of ulcer were distributed, according to weight Then the mean blood pressure for persons of all builds in the control group ( $s$ ) was divided by the average ( $r$ ) The quotient represented the correction for weight ( $z$ ) The figure represented by  $z$  usually fell close to 1 If, in the cases for which correction was being made, there was a tendency to obesity,  $z$  would be less than 1, for example, 0.997 If, however, the tendency was to emaciation,  $z$  would be greater than 1, for example, 1.004 This calculation also made correction for age at the same time, since each result involved all cases in a certain age group Throughout the study, the various age groups were made up of persons who fell within the same upper and lower limits according to age The following example shows the correction of data for age and weight

		Disease	Control
		Group,	Group,
		Fre-	Blood
		quency	Pressure
			Means
Age Group, Years 25-29	Thin	$a$	$\times n = an$
	Normal	$b$	$\times o = bo$
	Stout	$c$	$\times p = cp$
		$d$	$m$

$m + d = r$ ,  $s - r = z$  ( $s$  = mean of control cases, all builds,  $z$  is the "weight correction")

$z \times \text{mean of group being corrected} = \text{"corrected mean"}$

In order to make the comparison fairer, three additional groups were studied One of these comprised 1,685 cases of cholecystitis In 782 cases in this group, cholelithiasis was present The data were corrected for age and weight against the control group, and were compared with those in the cases of ulcer Since the data in the ulcer group and in the group of cases of disease of the gallbladder were corrected with those of the same control group, it is not significant whether or not the control group was normal

The second of the three additional groups to undergo analysis was made up of 571 cases of inoperable carcinoma of the stomach and 239 cases of carcinomatous gastric ulcers, the data were corrected for age and weight. The cases of inoperable carcinoma selected because of the patients' low systemic resistance had all been proved by the surgeon to be inoperable.

The third of the three additional groups was made up of cases the reports of which were obtained from one life insurance company<sup>1</sup>. We did not use the "normal blood pressure curve" that was used by the company, but derived averages, by calculation, from the frequency distribution of the various blood pressures in five-year age groups of

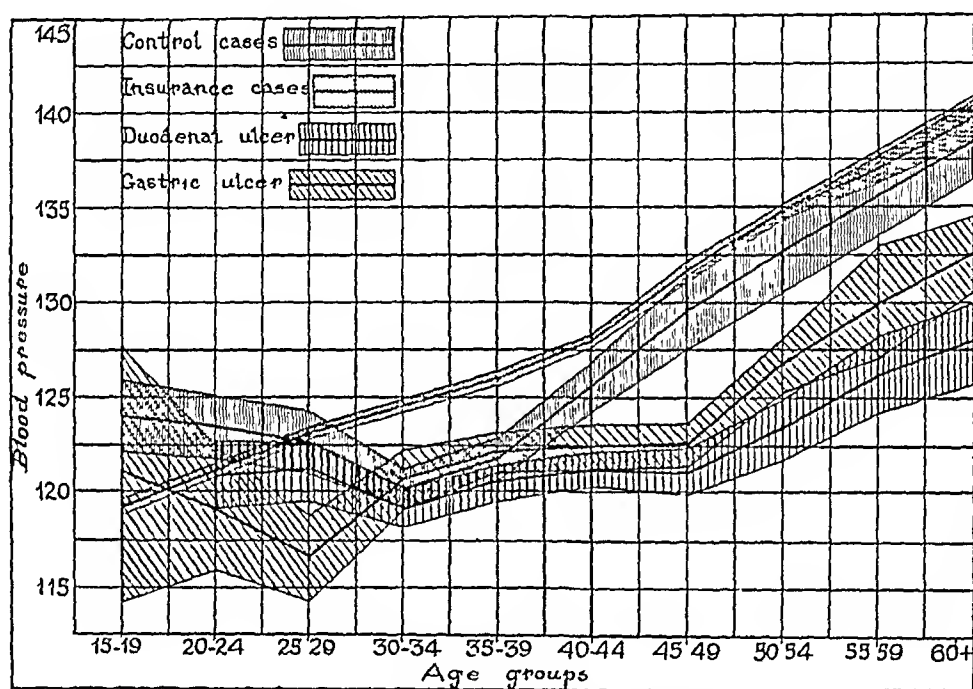


Chart 1—Systolic blood pressure in cases of duodenal and gastric ulcers compared with blood pressure in control cases and life insurance cases (males)

all persons who applied for life insurance during a given period. This group contained 4,209 men and 1,518 women, and included some persons who had been rejected and others with abnormal blood pressure. The averages that were derived correspond fairly well with other averages obtained from life insurance tables<sup>2</sup> and from army statistics,<sup>3</sup>

1 Furnished by W. G. Exton, director of laboratories and longevity service, Prudential Life Insurance Company of America.

2 Hunter, Arthur, and Rogers, O. H. Blood Pressure as Affected by Sex, Weight, Climate, Altitude, Latitude or by Abstinence from Alcoholic Beverages, *Assn. Life Insur. Med. Directors of America* 6:92, 1919-1920.

3 Fleming, W. D. Blood Chemistry and Blood Pressure Standards. I. The Effect of Tropical Residence on the Blood Chemistry and the Blood Pressure. *J. Metab. Research* 6:87, 1924.

except that the derived averages were a little higher in the later years of life, especially in women. Nevertheless, the derived average seems to give a fair "average blood pressure." Whether or not the derived average can be called normal is a question. We were unable to correct this group for weight because the height and weight were not available in each case in the series.

All material was divided according to sex, and arranged in five-year age groups. The mean blood pressures with their probable errors and

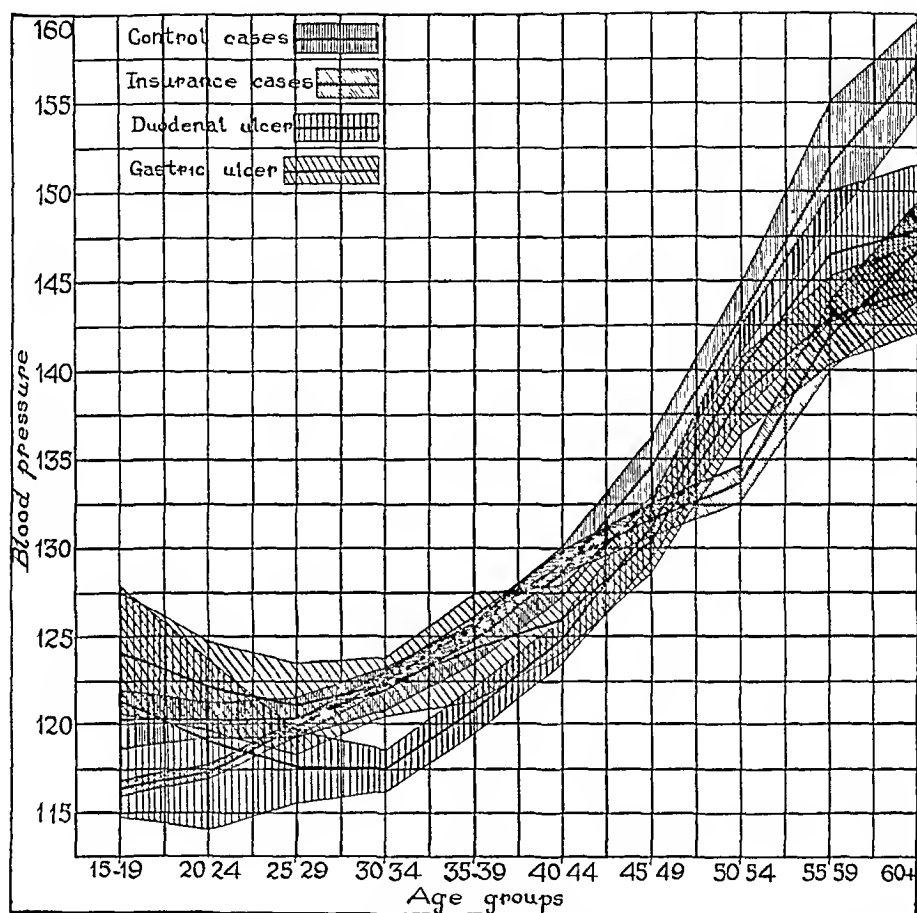


Chart 2—Systolic blood pressure in cases of duodenal and gastric ulcers compared with blood pressure in control cases and life insurance cases (females)

standard deviations were calculated for all of the age groups. All of the curves were smoothed, and the probable errors are shown in charts 1, 2, 4, 5, 6 and 7. The plus and the minus errors are shown respectively, by the shaded areas above and below the middle line which represents the actual mean.

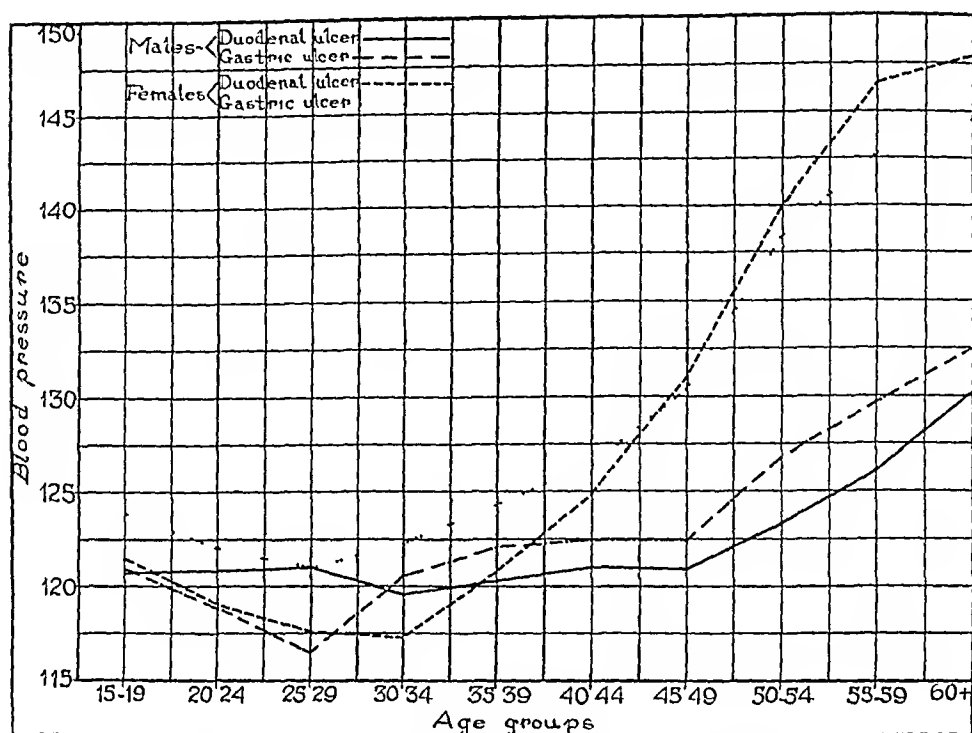


Chart 3—Systolic blood pressure in cases of gastric and duodenal ulcers (males and females)

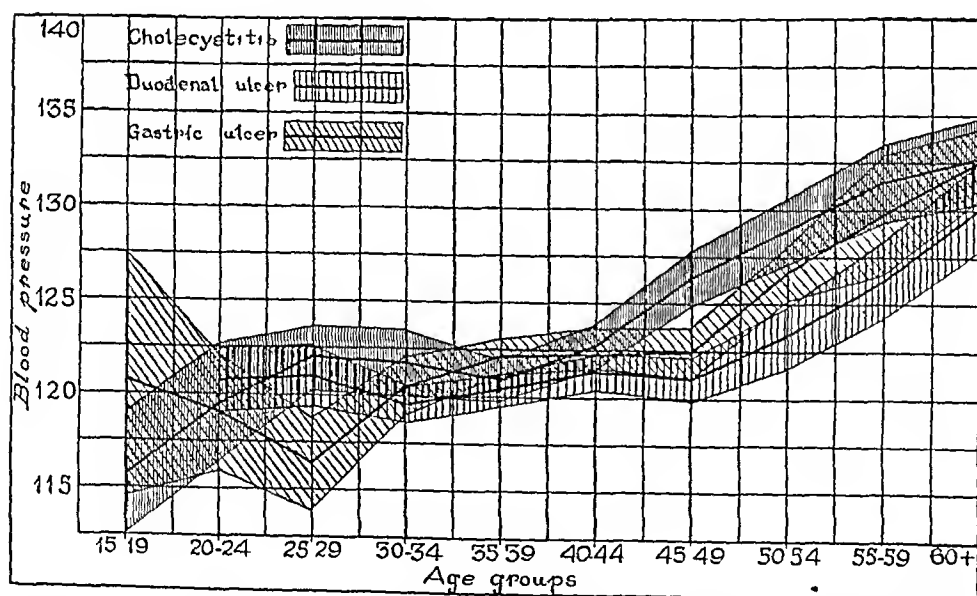


Chart 4—Systolic blood pressure in cases of duodenal and gastric ulcers compared with blood pressure in cases of cholecystitis (males)

In chart 1, constructed from statistics derived from male patients, the difference between the curve of blood pressure, as derived from the insurance figures, and that in cases of duodenal ulcer, varies from 0.3 to 11.4 mm, in the cases of duodenal ulcer the systolic blood pressure falls below that of the insurance cases. From the ages of 30 to 59, the difference between the mean blood pressure in the insurance group and the corrected mean in the duodenal ulcer group, divided by its probable error, is 4.9 or more, with 1,052 or more chances to 1 that the difference is significant<sup>5</sup>. The blood pressures in the cases of gastric ulcer in

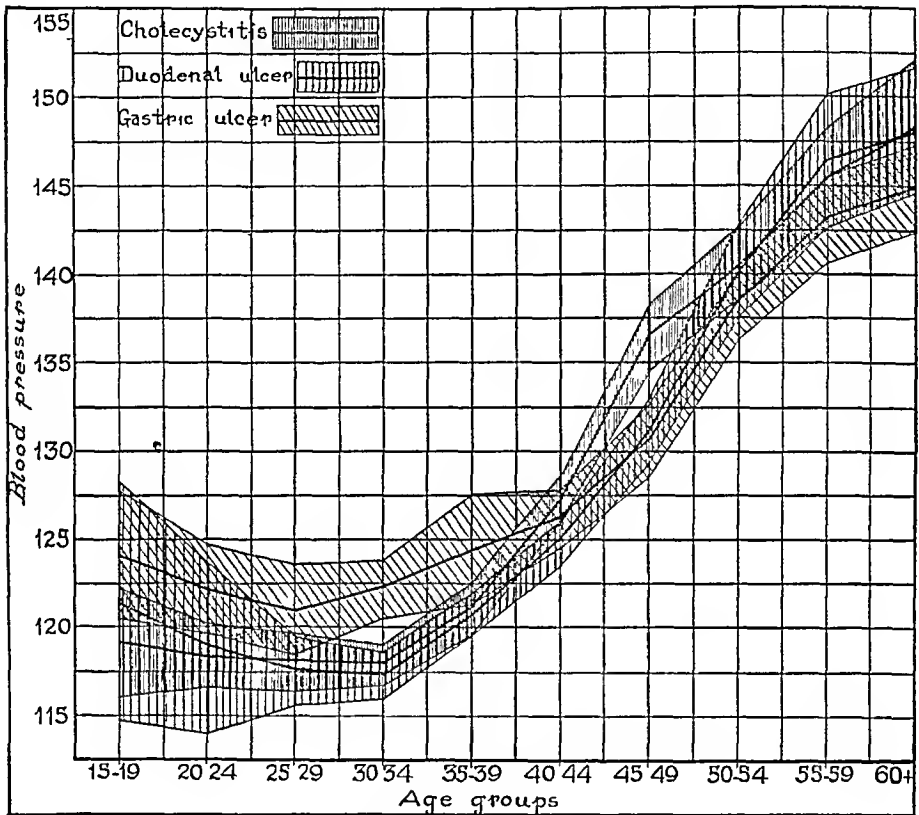


Chart 5—Systolic blood pressure in cases of duodenal and gastric ulcers compared with blood pressure in cases of cholecystitis (females)

males do not show such a marked fall as those in cases of duodenal ulcer, the difference between the blood pressures in this group and in the insurance group varies from 1.8 to 9 mm, and shows a significant difference only between the ages of 45 and 59. The difference between the blood pressure in the control cases and in cases of duodenal ulcers in males varies from 0.6 to 9.3 mm and is not significant at any point. Comparison of the cases of gastric ulcers with the control cases, in

<sup>5</sup> Pearl, Raymond. Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, 1923, p. 209.

males, shows even less difference in blood pressure, it ranges from 0.1 to 7.2 mm, and has no significance. The blood pressures in the control cases have a tendency to drop at from 25 to 35 years of age, this tendency is similar to that seen in the cases of gastric and duodenal ulcer, although cases of ulcer were excluded from the control group. On the other hand, the blood pressure curve of the life insurance cases rises steadily throughout.

In chart 2, which applies to female patients, there is not a point in the whole curve in which the difference in blood pressure is significant between the cases of duodenal or gastric ulcers and the life insurance cases. Unlike that in the males, the curve of the mean blood pressure

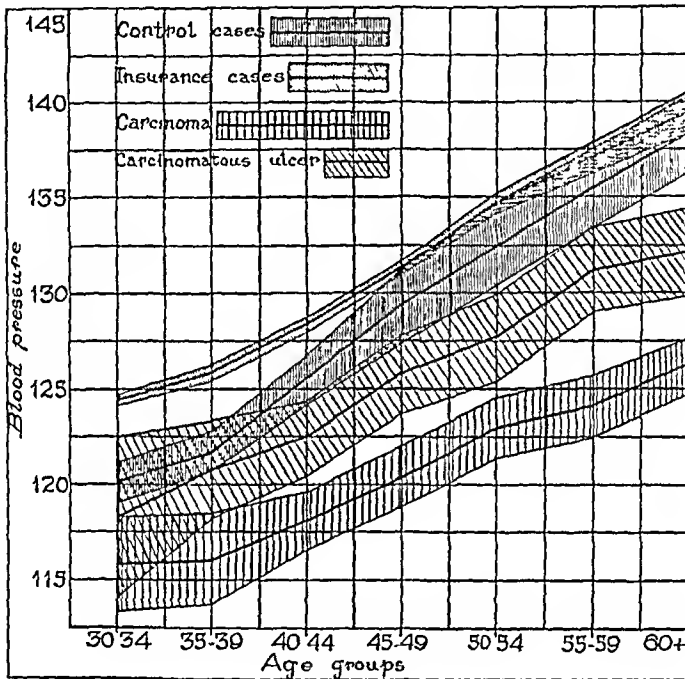


Chart 6—Systolic blood pressure in cases of carcinoma of the stomach and carcinomatous ulcers compared with blood pressure in control cases and life insurance cases (males)

even rises above the one shown in the insurance curve at some points. Comparing the blood pressures in females with duodenal or gastric ulcer with the blood pressures in the control cases results are obtained that are similar to those found when blood pressures in female patients with duodenal or gastric ulcer were compared with the insurance cases, except that the blood pressure in the control cases is higher in later years and has a tendency to rise above the blood pressure in cases of ulcer throughout the whole curve. Although in females in the control cases, there is not the drop in blood pressure from the ages of 25 to 35 that is seen in the control cases in males, the averages remain level up to the age of 30.

The wide difference between the mean blood pressures of the male and female patients with gastric or duodenal ulcer in the later years of life is marked (chart 3)

Charts 4 and 5 show the blood pressure in cases of ulcer compared with that in cases of cholecystitis. The difference between the blood pressures in these two groups varies from 0.2 to 5.7 mm., and is not great enough at any point to be of significance. The probable errors even overlap each other most of the way. The

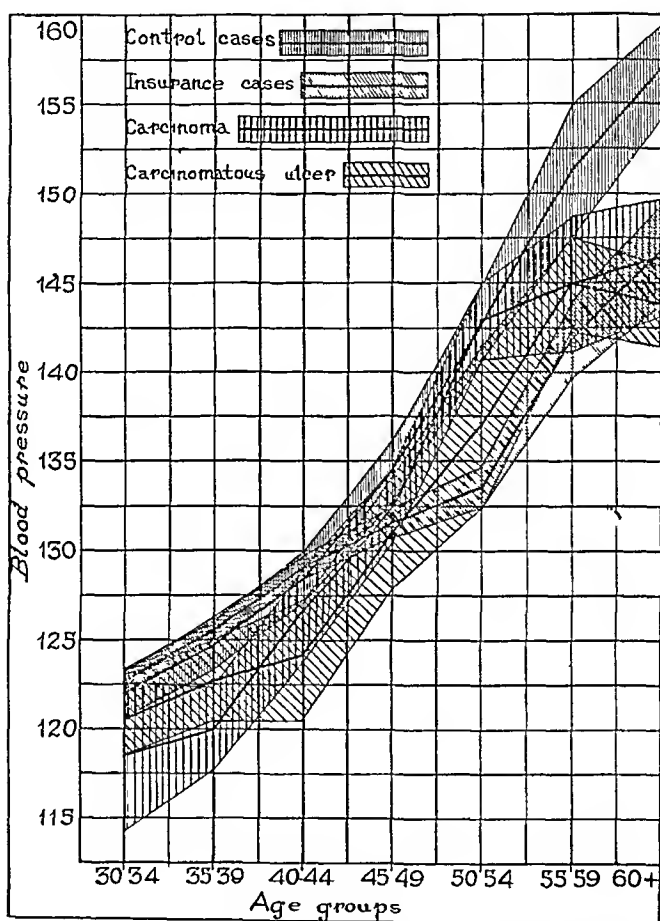


Chart 7—Systolic blood pressure in cases of carcinoma of the stomach and carcinomatous ulcers compared with blood pressure in control cases and life insurance cases (females)

data in charts 4 and 5 furnish, perhaps, the most severe test on which to make the comparison to determine whether or not the systolic blood pressure is lowered in cases of gastric and duodenal ulcer. In cholecystitis, blood pressure is expected to be higher because of the tendency to obesity and the plethoric body type that is usually characteristic of persons with disease of the gallbladder. If the blood pressure in gastric and duodenal ulcer, on the one hand, and in cholecystitis, on the other,

should prove to be about equal, the inference would be that the blood pressure in gastric and duodenal ulcer is not lower than the so-called average blood pressure. Although in males the blood pressures in the cases of ulcer tend to be lower than those in either the insurance or control cases, and although in females they tend in the cases of ulcer to be lower than those in the control cases, yet the blood pressures in cases of ulcer do not vary greatly from those in cases of cholecystic disease. The difference in blood pressure between the two groups ranges only from 0.2 to 5.7 mm. Patients with cholecystic disease show a tendency toward obesity and toward apparently higher blood pressure, but this figure is lowered through the correction for weight. On the contrary, in cases of ulcer the patient tended toward emaciation.

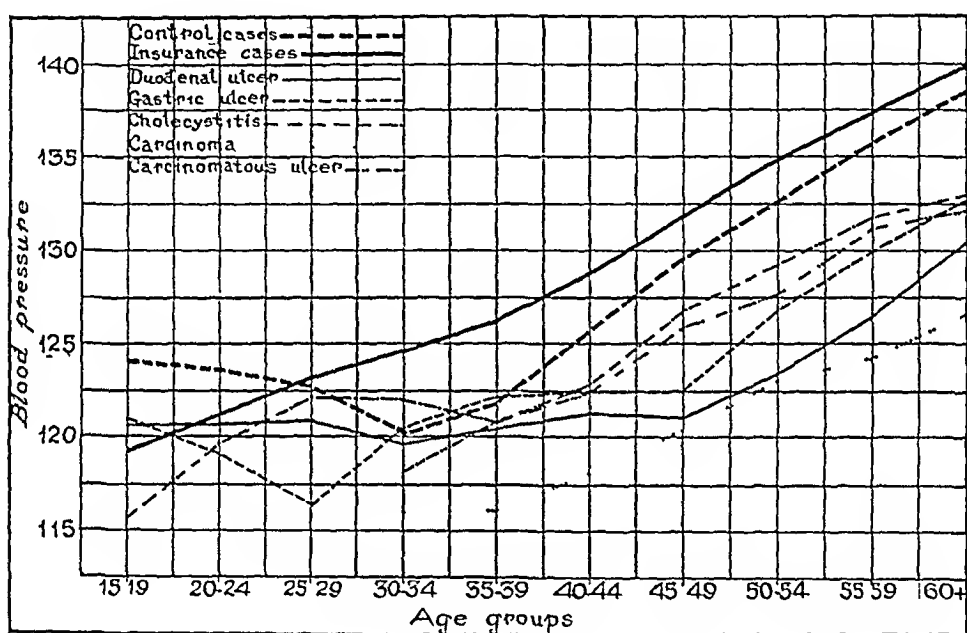


Chart 8—Systolic blood pressure in cases of duodenal and gastric ulcers, cholecystitis, carcinoma of the stomach, carcinomatous ulcers of the stomach, control cases and life insurance cases (males)

and so the figures representing their blood pressures were raised by the correction for weight. Therefore, the difference that did exist between the uncorrected curves for blood pressure in ulcer and in cholecystitis was narrowed considerably by the correction for weight.

Charts 6 and 7 present the mean blood pressure in cases of inoperable carcinoma of the stomach and of carcinomatous ulcer, compared with that in the life insurance and control cases. As in cases of ulcer, the blood pressure in males in the cases of carcinoma of the stomach is much lower than that in the insurance group (chart 6), the difference between the values in these two groups varies from 8.5 to 13.2 mm, which is significant from the age of 40 on. In carcinomatous ulcers,



the blood pressure is higher, falling not more than 7.4 mm below that in the insurance cases, and without significant differences in the whole curve. In comparison with the blood pressure in the control cases (from which the cases of carcinoma were excluded) there is a tendency to lower blood pressures in carcinoma, but this is of significance only in the last age group. The blood pressure curve in carcinomatous ulcer lies almost midway between that of the control cases and that of the cases of carcinoma of the stomach, and does not have any significant variation from the curve of the control cases.

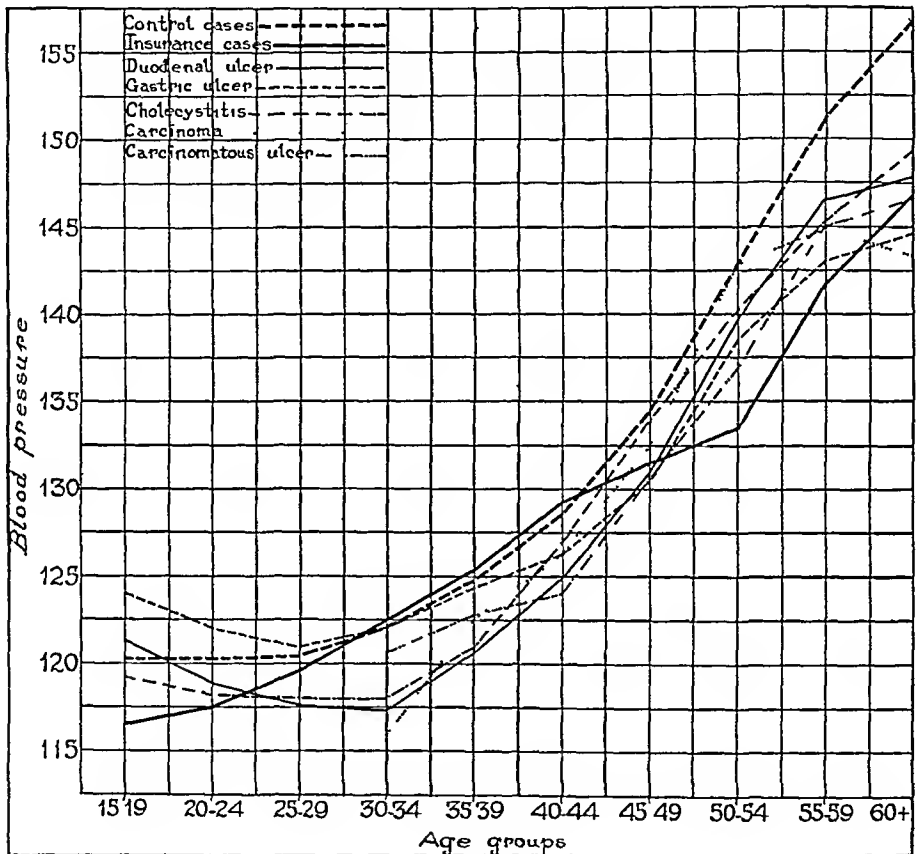


Chart 9—Systolic blood pressure in cases of duodenal and gastric ulcers, cholecystitis, carcinoma of the stomach, carcinomatous ulcers of the stomach, control cases and life insurance cases (females)

The blood pressures of the female patients with inoperable carcinoma of the stomach and with carcinomatous ulcers follows the life insurance curve closely, and even rises above it from the ages of 45 to 59. The difference between the blood pressures in the insurance group on the one hand, and in the carcinoma and carcinomatous ulcer group, on the other hand, varies from 0.2 to 9.3 mm and is not significant at any point. The mean blood pressure in the cases of carcinoma of the

stomach in females does not fall below that in the cases of carcinomatous ulcer, as it did in the males. The difference between blood pressure in cases of carcinoma of the stomach and that in the control cases varies from 0.1 to 13.6 mm, but is not significant because of the large probable errors. The blood pressures in cases of malignant ulcers vary less from those in the control cases, and the variations are not significant.

Chart 8 is a condensed graph drawn from the means of all of the blood pressure curves of the males. All of the curves are below that derived from the insurance cases from the age of 20 on, with the

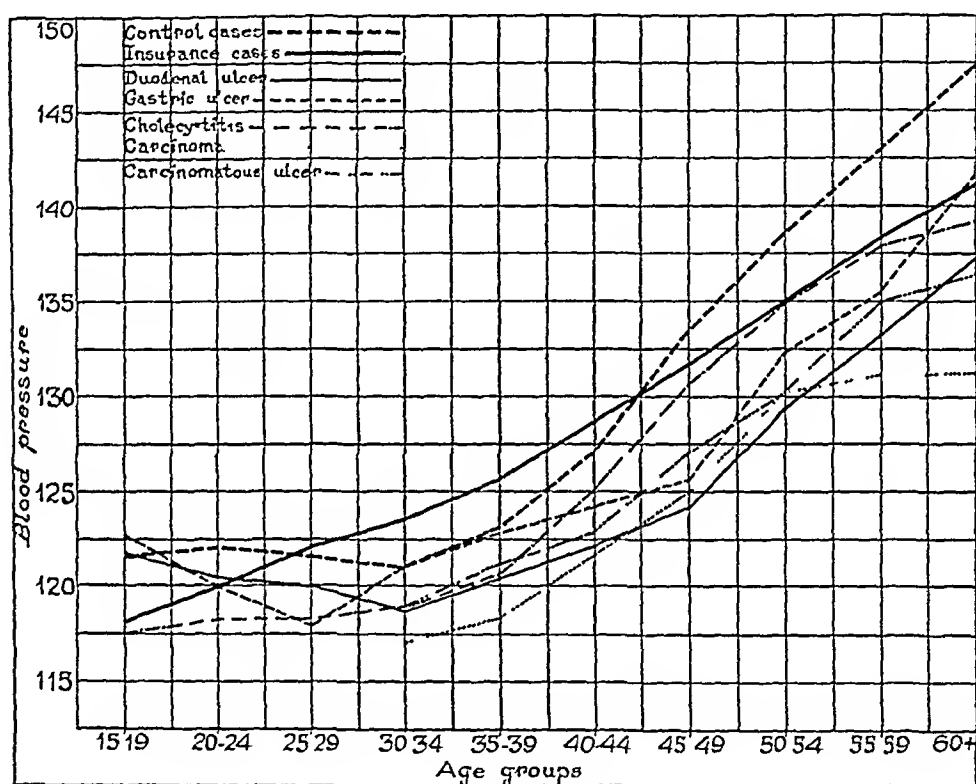


Chart 10—Systolic blood pressure in cases of duodenal and gastric ulcers, cholecystitis, carcinoma of the stomach, carcinomatous ulcers of the stomach, control cases and life insurance cases (males and females combined)

curves from the cases of carcinoma of the stomach and of duodenal ulcer falling lowest. The same tendency to low blood pressures in all of the groups of persons with disease shows up well on the graph, with a range of not more than 8 mm of difference between them. The curves also fall below those derived from the control cases, except for the ages from 30 to 40.

Chart 9 shows curves computed from the means of all of the blood pressure curves of the females. Here, as in chart 8, the same tendency exists among the curves of groups of patients with disease, all these curves adhere closely and rise above the insurance curve in the later

years of life, but they fall below the curves of the control cases except in the early years

Wide differences between the mean blood pressure of males and of females were found in the control cases, and in cases of cholecystic disease carcinoma of the stomach and malignant ulcer, as well as in cases of duodenal or gastric ulcer This difference would show up even more plainly if these curves were placed side by side with curves derived from examination of applicants for life insurance, in life insurance work, the average blood pressure of the females is not higher than that of the males In other words, in groups in which the majority of the subjects are diseased, blood pressures of the sexes vary, whereas in groups in which the majority of the subjects are healthy, this variation is not seen

Chart 10 shows curves constructed from the combined mean blood pressures of males and females in each of the various groups studied The largest difference between any two of these curves is 16.5 mm, all curves from the age of 25 on fall below that constructed from the life insurance material, and from the age of 35 on below that of the control cases The low tendency prevails because of the fact that there were more males than females in all of the groups studied except in the group with disease of the gallbladder

#### SUMMARY

The blood pressure in cases of duodenal and gastric ulcer, compared with the curve constructed from life insurance statistics, is lower in males and in the sexes combined, but it is not lower in the females alone Too much stress, however, cannot be placed on this comparison, because of the fact that the insurance cases were not corrected for weight, and the other groups were not corrected against a normal blood pressure, but against a control group The blood pressures in this control group also are higher than those in the ulcer group in both males and females, but the variation is not of significance, the curves remain fairly parallel throughout all ages

In comparing the blood pressure in cases of duodenal and gastric ulcer with that in cases of cholecystitis and carcinoma of the stomach or carcinomatous ulcer, the difference is not significant in either males or females From this it must be concluded that in cases of ulcer the blood pressure is not particularly low, and is similar to that in other diseases of the alimentary tract It might have been better to make the comparisons with other than gastro-intestinal diseases, but it would seem that the inclusion of a series of cases of cholecystic disease for comparison establishes the results as reliable, since the impression is almost universal that patients with cholecystitis have a tendency toward higher blood pressure

If the data had not been corrected for weight, the results would have been somewhat different, and the comparison between the cases of ulcer or carcinoma with the cases of disease of the gallbladder might have been significant. The correction for weight, however, must be given consideration, for age and weight play an important part in the readings of blood pressure.

# INFLUENCE OF THE DIAPHRAGM ON THE ESOPHAGUS AND ON THE STOMACH <sup>1</sup>

MINAS JOANNIDES, M D  
CHICAGO

In the anesthetized dog, two different types of contraction were noted when the cardia was examined by the insertion of the finger into the esophagus through a gastrostomy opening <sup>1</sup>. One type of contraction (the esophageal) was circular and constricting, it was reproduced at will by stimulation of the peripheral end of the vagus, and also by stimulation of the esophagus itself at any level above the gastro-esophageal junction. The second type, which was due to the contractions of the diaphragmatic pillars, was a progressively downward milking contraction and was coincident with each inspiration. The diaphragmatic contraction became more pronounced when diaphragmatic breathing became more forcible. The maximum contraction was noticed when the diaphragmatic crura were stimulated with the faradic current.

Clinical evidence of a relationship of the diaphragm to the cardia was brought out by Chevalier Jackson <sup>2</sup> and Tucker <sup>3</sup>. Jackson stated that the "diaphragmatic pinchcock or hiatal narrowing is both anatomical and functional. The peculiar arrangement of the tendinous and muscular structure of the diaphragm acts on this hiatal opening, pinching the esophagus shut in a way similar to that of the pinchcock that closes the rubber tube of the burette in the laboratory. There are also special bundles of muscle fibers extending from the crura of the diaphragm and surrounding the esophagus, which contribute to the tonic closure and the coordinate opening in the deglutitory cycle and probably also in the emetic cycle." In an anatomic dissection of the diaphragmatic crura in the dog and in the human being, several important facts have been noticed. There is a more intimate relationship between the diaphragm and the gastro-esophageal junction (cardia) than is generally shown in illustrations of anatomic monographs and texts. The structure of the muscle fibers in the diaphragmatic pillars bears a greater resemblance

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<sup>1</sup> Submitted for publication, June 3, 1929

<sup>2</sup> From the Department of Surgery, University of Illinois College of Medicine

1 Joannides, Minas. The Relation of the Hiatus Esophageus of the Diaphragm to the Stomach, *Arch Int Med* **43** 61 (Jan) 1929

2 Jackson, Chevalier. The Diaphragmatic Pinchcock in So-Called Cardiospasm, *Laryngoscope* **32** 139, 1922, *Bronchoscopy and Esophagoscopy*, ed 2, Philadelphia, W. B. Saunders Company, 1922, pp 71, 73 and 333

3 Tucker, G. Diaphragmatic Pinchcock in Health and Disease, *M Clin North America* **8** 931, 1924

to the anal sphincter than it does to the rest of the diaphragm. A thin layer of areolar tissue separates the pillars from the cardia. This areolar tissue is definite in the human being and produces a definite line of cleavage between the esophagus and the pillars. On the other hand, in the dog this layer is very thin, so that one receives the impression that the fibers of the pillars are in direct apposition with the cardia. Anteriorly the muscle fibers of the pillars surround the stomach and esophagus in a manner similar to the fibers of the anal sphincter. As these fibers extend posteriorly to the esophagus and stomach, they decussate and become attached to the vertebrae. At the point of decussation the pillars form an inverted triangle which is small in the dog and from 1 to 2 cm wide in the human being. The sides of this triangle are joined together by means of thin fibrous tissue. It is through this fibrous tissue that air may find its way from the mediastinum to the retroperitoneal tissues in mediastinal and interstitial emphysema.<sup>4</sup> Regarding the relation of the so-called cardiospasm to the diaphragm, Jackson stated that the so-called cardiospasm probably covers a number of diseased conditions, some functional, others organic, but none of them at the cardia. He gave a number of terms for cardiospasm in an attempt to specify more clearly the mechanism of the syndrome. So-called cardiospasm, according to Jackson, may be called preventriculosis, ingluviosis, functional hiatal stenosis, hiatal esophagismus, phrenospasm and diaphragmatic pinch-cock stenosis. Jackson found "no sphincteric muscular arrangement at the cardiac orifice of the esophagus, so that spasmodic stenosis at this level is not possible and the term cardiospasm is, therefore, a misnomer." The observations of Jackson were corroborated by Mosher and McGregor.<sup>5</sup> In cases of so-called cardiospasm they found a fibrosis in the pillars, an absence of an anatomic sphincter of the cardiac end of the esophagus and a decrease of the ganglion cells of Auerbach's plexus.

Although this study bears a definite relation to the mechanics of so-called cardiospasm, it deals primarily with the rôle played by the diaphragm in the normal contraction and relaxation of the cardia, in the mechanics of belching and in the induction of peristaltic contractions in the stomach.

#### EXPERIMENTAL WORK

Observations were made by placing a normal subject in an oblique upright position with the right shoulder placed against the fluoroscopic screen, after the method described by Carman.<sup>6</sup> A barium meal was

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4 Joannides, M., and Tsoulos, G. Experimental Production of Mediastinal and Interstitial Emphysema in the Dog, to be published.

5 Mosher, H. P., and McGregor, G. W. A Study of the Lower End of the Esophagus, *Ann Otol Rhin & Laryng* **37** 12 (March) 1928.

6 Carman, R. D. The Roentgen Diagnosis of Diseases of the Alimentary Tract, ed 2, Philadelphia, W. B. Saunders Company, 1921, p. 44.

then given. When the barium was seen to reach the cardia the patient was asked to breathe deeply. With each inspiration the esophagus was constricted at the cardia to such a degree that no barium could be seen below the diaphragm. A ballooning of the filled esophagus resulted above this constriction. This constriction and ballooning corresponds, in certain respects, with the roentgen pictures of so-called cardiospasm. It also no doubt corresponds with the terminal phase of the downward milking contraction in the cardia of dogs that was observed by insertion of the examining finger through an opening in the stomach. This contraction, however, is transitory, because with the onset of the expiratory phase of respiration the diaphragm was noticed to rise and, coincidentally with this relaxation, the barium ran freely again into the stomach. This phenomenon could be repeated as often as desired in the same patient or in different patients. Some variations were noticed, depending on the movements of the diaphragm and the tendency of the patients to dyspnea. In persons who could hold their breath fairly long, the barium remained above the diaphragmatic level longer than in those who could not. In persons who showed hypertonicity and a tendency to spasm there was a delay in the course of the barium at the cardia even during expiratory relaxation. If the patient was asked to take a few deep breaths, thus inducing milking contractions at the pillars, this spasm could be relieved and the barium found its way into the stomach. If the barium meal was distasteful to patients and there was fluoroscopic evidence of a tendency to nausea and vomiting, relief was given by making the patient take a few long deep breaths. After a few deep breaths, he showed a normal condition in the esophagus, diaphragm and stomach.

With the introduction of barium into the stomach in the majority of patients, a large air bubble finds its way into the stomach. With the patient in the erect position the air bubble floats on the surface of the gastric fluids and distends the fundus. This phenomenon afforded an opportunity for study of the mechanism of belching as seen with the fluoroscope. When the patient made a conscious effort to belch, the costal portion of the diaphragm contracted and the vertebral portion relaxed. In the meantime, the abdominal muscles contracted and squeezed the stomach, at the midportion of which a constricting band had developed by this time, causing it to assume the shape of an hour-glass. When the patient was ordered to belch again, one could see a series of peripheral diaphragmatic contractions and a relaxation of the vertebral portion with the air moving away from the dome of the fundus and closer to the cardiac opening. Jackson mentioned the presence of a "kink of the esophagus" which normally prevents regurgitation when a man with a full stomach stands on his head or inverts his body.

That such a deflection or kink is present can be demonstrated by watching the course of the barium through the esophagus into the stomach. The barium travels straight downward, deviating slightly at curves of the spine, when it reaches the cardia it suddenly deflects from its course along the spine in an angle of from 30 to 50 degrees. It is possible, therefore, that in belching the contractions of the diaphragm push the fundus down and medially and thus release the kink that is formed at the junction of the cardia and the fundus.

In some cases in which repeated attempts at induced belching failed, it was noticed that the whole left side of the diaphragm would relax for a moment and at the same time the right side would contract coincidentally with the contractions of the abdominal wall and stomach. Contractions and relaxations of the diaphragm, as seen normally with inspiration and expiration, have no apparent relation to belching. No belching occurred either with deep inspirations or with forcible expirations. Similarly the air in the fundus could not be squeezed out by manual pressure over the abdomen. If a stomach tube was passed into the stomach, under such circumstances, air could be readily squeezed out. This observation has an important clinical application. Under varying conditions during an operation the stomach may become so distended with air that any external pressure over the exposed stomach will not force the air out. On the contrary, it may cause injury to the wall of the tensely distended organ. A tube introduced into the stomach from above will promptly cause the air to run out from the stomach, at times even without compression over the organ. Kelling<sup>7</sup> found the same condition in dogs under deep anesthesia. This phenomenon may be regarded as corroborative evidence that the constriction is due to a spasm of the diaphragmatic pillars in the region of the cardia, provided one assumes that Jackson's or Mosher and MacGregor's observation is correct, namely, that there is a pinchcock phenomenon or that there is no actual sphincter in the esophagus at the cardia.

After the barium reaches the stomach, one can induce prompt contractions in the organ by having the patient take deep breaths. Such peristaltic waves in the stomach may be central in origin and induced reflexly from cross stimuli from the respiratory center to the vagus center. It appears more reasonable to assume, however, that such an induction of peristalsis in the stomach depends on the milking contractions in the pillars with the impulses probably extended along the wall of the stomach or perhaps is due to the intermittent increase and decrease of intragastric pressure induced by the contractions of the diaphragm.

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<sup>7</sup> Kelling, G. Ueber den Mechanismus der acuten Magendilatation, *Arch f klin Chir* 64 393, 1901.



## COMMENT

The experimental work on the anesthetized dog and the clinical results with the fluoroscopic examinations of normal patients show convincingly that the diaphragm plays an important rôle in the mechanics of contractions and relaxations of the esophagus at the cardia

The classic work of Cannon<sup>8</sup> on the activities of the esophagus must be mentioned. He stated that two activities of the cardiac sphincter are to be distinguished—a persistent state of tonus, and, at times superposed on this, rhythmic alternation of contraction and relaxation. He further stated that “normally we are unconscious of the nauseating odor and the highly disagreeable taste of the gastric contents, and for this pleasant security the closed cardia is highly responsible. As aids in establishing this barrier between the stomach and the gullet, the sharp angle between the two structures, acting like a valve, and the close grasp of muscle layers in the diaphragm have been mentioned.”

The present results are not in accord with the assumptions of Alvarez.<sup>9</sup> After mentioning the work of Gubaroff, Kelling, Sinnhuber and Caballero, who felt that a large part of the sphincteric action at the cardia must be due to the contraction of the diaphragmatic fibers surrounding the lower end of the esophagus, he stated that “this now seems improbable because it can be seen with the roentgen ray that the sphincter is generally situated some two centimeters below that point.” Alvarez did not state how he determined the presence of such a sphincter below the diaphragm. The dissection of cadavers and dogs in the present experiments showed that the pillars are directly over the junction of the stomach and esophagus. The fluoroscopic observations corresponded with the bronchoscopic observations of Jackson and Tucker. Knowing from digital examinations of the esophageal orifice that there is a milking contraction, and seeing the extent of such a contraction under the fluoroscope, I feel justified in assuming that Jackson’s pinchcock contraction of the diaphragm is probably only one phase of a complex contraction.

The rôle of the diaphragm in voluntary belching is of great interest. The peculiar contractions of the costal fibers of the diaphragm tend to straighten the kink just below the cardia and allow the air to be squeezed out. These peripheral contractions probably also induce a pull on the vertebral portion of the diaphragm and thus cause a dilatation of the pillars. Coincident with these contractions, the abdominal muscles and the stomach induce belching. It is interesting to note that when a barium meal is taken (1 part barium sulphate and 3 parts malted milk plus

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8 Cannon, W. B. *The Mechanical Factors of Digestion*, New York, Longmans, Green & Company, 1911, p. 33.

9 Alvarez, W. C. *The Mechanics of the Digestive Tract*, ed. 2, New York, Paul B. Hoeber, 1927, p. 91.

water), invariably a large air bubble enters the stomach and promptly lodges itself in the fundus immediately under the diaphragm. Thus air undoubtedly stays lodged either in the esophagus or in the buccal cavity and is pushed down into the stomach by the weight of the fluid. Repeated examinations before a barium meal failed to show the presence of air in the empty stomach. Therefore, this air must necessarily come from above the stomach. It is undoubtedly this same phenomenon that one encounters in the feeding of infants. A gas bubble enters the stomach of an infant and may distend the stomach causing colic or prevent the child from taking the necessary amount of milk at each feeding. A roentgenologic study of infants during feeding and immediately afterward may solve the problem of finding a means to expel swallowed air by more reliable methods than those in present usage.

#### SUMMARY

1 Two types of contraction can be observed by a digital examination of the cardia, namely, a circular constricting contraction and a downward milking contraction.

2 Fluoroscopic examination of the course of barium in the stomach reveals an obstruction in the region of the cardia coincident with each inspiration, and a relaxation with release of the obstruction with each expiration.

3 The obstruction noticed fluoroscopically may correspond to a single phase of the downward contraction and is, no doubt, identical with the pinchcock contraction described by Jackson.

4 Belching is accomplished by the coordinate contraction of the abdomen, the stomach and the costal end of the diaphragm, with the relaxation of the vertebral end.

5 Spasm of the diaphragmatic pillars with obstruction and dilatation of the esophagus may be relieved by deep inspirations and expirations.

6 Acute sudden gaseous distention of the stomach in patients during operations under ethylene, nitrous oxide or ether anesthesia may be easily relieved by intubation of the stomach.

7 Gastric peristalsis was noticed to start as a result of deep breathing.

8 So-called cardiospasm may be an exaggeration of the normal contractions of the diaphragmatic pillars. A persistent spasm of these bundles will, no doubt, cause a chronic obstruction at the cardia.

# OPIUM ADDICTION

X THE EXCRETION OF MORPHINE BY HUMAN ADDICTS \*

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The relation between the capacity of the animal body to destroy morphine and its power of developing tolerance to the drug following repeated dosage has been of interest to pharmacologists for many years. Recent study with the aid of improved chemical methods indicates that Faust's<sup>1</sup> conclusion, that a direct, casual relationship between the two phenomena exists, is incorrect. It seemed important to collect from human material such data as might bear on this subject. The study here reported concerns the excretion of morphine by human addicts, the difference between the amounts of morphine administered and those excreted is to be regarded as a measure of morphine destroyed.

While it is well known from the early observations of Kauzmann,<sup>2</sup> Vogt,<sup>3</sup> and Jacques<sup>4</sup> that morphine is eliminated in the urine and feces of human addicts, its quantitative excretion in these channels has, to our knowledge, not been studied. In the subjects whom we have studied it has been possible to control reliably the morphine dosage, to vary this at will and to collect the excreta quantitatively. In addition to observations on the (healthy) subjects of uncomplicated addic-

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\* Submitted for publication, Sept 13, 1929

\* From the Narcotic Wards of the Philadelphia General Hospital and the Laboratory of Pharmacology, University of Pennsylvania

\* Expenses of this research were defrayed by the Committee on Drug Addictions, New York City, and this work carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction, in the wards of the Philadelphia General Hospital, which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia, and also the Laboratory of Pharmacology of the University of Pennsylvania

1 Faust, E S Ueber die Ursachen der Gewohnung an Morphin, *Arch f exper Path u Pharmacol* **44** 217, 1900

2 Kauzmann Beitrage fur den gerichtlich chemischen Nachweis des Morphins und Narkotins in thierschen Flussigkeiten und gemeinen, Inaug Dissert, Dorpat, 1868 Cited by Faust (footnote 1, p 223)

3 Vogt *Arch d Pharm* **7** 23 (July) 1875

4 Jacques These Bruxelles, 1880, Essai sur localization des alcooloides dans le foie, cited by Faust (footnote 1, p 224)

tion, we had the opportunity of measuring the elimination of morphine, on constant dosage, during the periods of fever, crisis and convalescence in one addict who was acutely ill with pneumonia

#### METHODS AND PROCEDURE

As soon as possible after admission the predetermined morphine regimen was established. The daily dosages of morphine chosen were 15, 30 and 60 grains (0.97, 1.94 and 3.89 Gm.), and a period of four days was ample to establish any one of these levels, regardless of the amounts which had been taken before admission or the form of the drug used. Experimental periods usually lasted for five days, although one case was studied for only three days and another for four days. No attempt was made to control the diet, nor were any other drugs administered except an occasional saline cathartic to obtain a bowel movement.

Morphine in urine was determined by extraction with chloroform-alcohol solvent, purification through further extractions and final precipitation with silicotungstic acid<sup>5</sup>. When the quantity of morphine in the final extract was less than 10 mg., it was estimated colorimetrically by the diazo-reaction<sup>6</sup>.

The suitability of this procedure for human material was shown by a series of control experiments. From 100, 200, 250 and 280 cc volumes of normal urine, analyzed gravimetrically, recoveries of added morphine were from 92 to 97.7 per cent. The morphine silicotungstate yielded, after ignition, from 70 to 70.3 per cent of oxide residues, an indication of the almost complete purity of the morphine precipitate. Similar controls containing no morphine showed negligible turbidity with silicotungstic acid. Colorimetric control experiments gave from 98 to 100 per cent recoveries of added morphine, with satisfactory blanks. These results were obtained only after meticulous attention to detail, as described by one of us (W. A. W.)<sup>7</sup> in a study of the elimination of morphine in dogs. The numerous possibilities of error in morphine analysis made it necessary to check and recheck every step in the procedure at frequent intervals.

Many of the specimens of urine were analyzed both colorimetrically and gravimetrically. Typical results shown in table 1 indicate the consistency of the two methods.

Feces, after preliminary acidification and evaporation over the steam bath, were analyzed as previously described<sup>5</sup>. Results on control determinations were variable and unsatisfactory. Hence, the figures presented for fecal excretion are hardly more than qualitative indications that a relatively small amount of morphine appears in the feces.

#### RESULTS AND COMMENT

Table 2 contains the results of the quantitative excretion of morphine in the urine and feces of a series of addicts receiving 15, 30 or

5 Balls, A. K., and Wolff, W. A. The Determination of Morphine, *J Biol Chem* **80** 379 (Dec.) 1928.

6 Lautenschlager, L. *Arch d Pharm* **257** 13, 1919. Plant, O. H., and Pierce, I. H. Excretion of Morphine During Gradually Produced and Prolonged Tolerance to Morphine in Dogs, *J Pharmacol & Exper Therap* **31** 212 (June) 1927.

7 Wolff, W. A. The Elimination of Morphine in Dogs, to be published.

60 grains per twenty-four hours Sixteen studies were made on ten different patients One patient (case 3-29) was studied on all three levels he eliminated 7.9, 8.2 and 10.3 per cent, respectively, in the urine Cases 10-29 and 2-29 were each studied on two different levels The patient in case 10-29 eliminated 8.6 per cent in the urine while receiving 30 grains, and 7.7 per cent on a 60 grain level Likewise in case 2-29 there was little variation in the percentage of morphine eliminated While receiving 15 grains he excreted 10.1 per cent, and while receiving 60 grains, 12.2 per cent

Case 6-29 was studied on the same level of 30 grains at two different intervals, with the elimination of 8.8 and 9.5 per cent of the morphine administered

Five patients who were maintained on 15 grains (0.97 Gm) daily varied from 6.5 to 10.1 per cent of excretion Urinary excretion of morphine for seven patients on a constant dosage of 30 grains ranged

TABLE 1—*Comparative Results of Colorimetric and Gravimetric Methods in Analysis of Urine for Morphine*

Case	Colorimetric Method, Mg per 100 Cc	Gravimetric Method, Mg per 100 Cc
5-29	4.7	4.1
12-29	32.7	32.0
4-29	6.1	7.8
10-29	8.2	9.3
10-29	15.0	15.3
3-29	9.2	8.4
3-29	22.0	18.8

from 8.2 to 12.9 per cent Morphine recovered from the urine of four patients receiving 60 grains per day varied from 7.7 to 12.2 per cent It may be noted that the percentage of morphine eliminated in the feces analyzed never exceeded one-fourth the urinary percentage Absolute values were too uncertain and variable to justify general conclusions

The results obtained in the foregoing experiments on healthy addicts show that regardless of the amounts taken, the fraction eliminated in the urine is remarkably constant Averages of the percentage of urinary excretion on the 60, 30 and 15 grain dosages amounted to 10.7, 9.8 and 8.7 per cent, respectively The fraction eliminated bears no relation to height, weight, volume of urine or length of addiction, but is directly proportional to the quantity administered These results show clearly that in human addicts the amount of morphine destroyed is proportional to the amount absorbed Despite the existence of mechanisms for the disposal of morphine, there must still be present in the addict an increased tissue tolerance, since the patients receiving 60 grains a day were eliminating in the urine approximately

6 grains (0.388 Gm), and those on 30 grains approximately 3 grains (0.194 Gm)

The lethal dose of morphine for man is not definitely stated in textbooks of pharmacology. Kunkel<sup>8</sup> quoted the minimal lethal dose as 1½ grains (0.097 Gm), but added that under favorable circumstances a person might recover from 15 grains. He regarded, however, the prognosis from a dosage of over 4 grains (0.259 Gm) as decidedly unfavorable. Sollmann<sup>9</sup> stated that the lethal dose ranges

TABLE 2—Data Obtained from Patients During Periods of Addiction

Case	Age, Years	Period of Study, Days	Average Weight		Average Daily Urine for Period, Cc	Daily Administration of Morphine		Average Daily Excretion			Feces, per Cent
			Pounds	Kg		Gm	Mg	Urine		Per Cent	
1-29	36	5	189	87.0	1,700	15	972	1.50	97	10.0	2.2
2-29	32	3	133	61.3	1,466	15	972	1.51	98	10.1	3.0
3-29	36	5	136	62.6	865	15	972	1.16	76	7.9	
4-29	39	5	113	52.0	1,217	15	972	1.17	77	7.9	
5-29	46	5	133	61.3	1,424	15	972	0.97	63	6.5	
6-29	35	5	122	56.2	2,332	30	1,944	3.24	168	8.8	
7-29	39	5	156	71.8	1,652	30	1,944	4.04	210	10.6	3.5
8-29	40	5	120	55.3	869	30	1,944	3.88	252	12.9	1.7
3-29	36	5	138	63.5	1,602	30	1,944	2.46	160	8.2	1.0
10-29	30	4	154	70.9	1,896	30	1,944	2.57	167	8.6	3.3
6-29	35	5	126	58.0	1,808	30	1,944	2.83	184	9.5	
9-29	34	5	150	69.1	2,841	30	1,944	3.14	204	10.5	
10-29	30	5	156	71.8	1,976	60	3,888	4.62	300	7.7	0.9
2-29	32	5	137	63.1	1,707	60	3,888	7.29	473	12.2	0.6
3-29	36	5	140	64.5	1,957	60	3,888	6.15	399	10.3	0.3
12-29	30	5	133	61.3	1,357	60	3,888	6.71	435	11.2	

TABLE 3—Morphine Recovered in Urine Following Abrupt Withdrawal of the Drug

Case	0-2 Hours, Mg	2-4 Hours, Mg	4-6 Hours, Mg	6-8 Hours, Mg	8-10 Hours, Mg	10-12 Hours, Mg	12-16 Hours, Mg	16-20 Hours, Mg	20-24 Hours, Mg	24-30 Hours, Mg
9-29*	40.1	11.5	9.6	8.5	6.6	4.9	5.6	5.0	4.0	11.2
6-29*	26.7	11.2	9.0	5.6	5.5	3.5	6.7	3.3	4.2	6.8

\* Received 30 grains (1.944 Gm) of morphine sulphate daily, 5 grains (0.324 Gm) at four hour intervals. The last injection was given at 9 a. m. The six hour period immediately following readministration of 5 grains (0.324 Gm) of morphine sulphate resulted in a recovery of 49.6 mg. in case 9-29, and in a recovery of 52.1 mg. in case 6-29.

between 3 and 6 grains, but mentioned one case of recovery from 60 grains. He also regarded the prognosis unfavorable when the dosage was more than 4 grains.

Table 3 and chart 1 contain the results of the analysis of urine collected at two hour intervals for the first twelve hours, four hour intervals for the second twelve hours and a final six hour period,

<sup>8</sup> Kunkel, A. J. Handbuch de Toxikologie, part 2, Jena, Gustav Fischer, 1901, p. 803.

<sup>9</sup> Sollmann, Torald. A Manual of Pharmacology, ed. 3, Philadelphia, W. B. Saunders Company, 1926, p. 300.

during thirty hours of abrupt withdrawal. In each case the last hypodermic injection of morphine sulphate given was 5 grains (0.324 Gm.).

The rate of elimination of morphine in the urine following the abrupt withdrawal in the two cases represented in both table 3 and chart 1 showed a rapid fall during the first four hours, after which a more constant level was maintained.

The rapid decrease in excretion during the first four hours was also noted in short period experiments for six hours following a dose of 5 grains of morphine sulphate. The morphine eliminated during the first two hours was three times that eliminated during the fifth and sixth hours. During withdrawal, the patient in case 9-29 eliminated 0.051 Gm., or slightly less than a grain, in the first four hours, 0.15 Gm. for the four to eight hour interval, or slightly more than

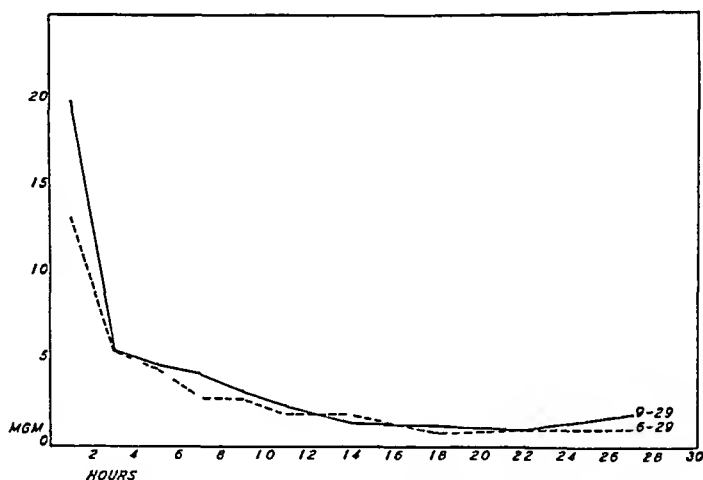


Chart 1—Curve of morphine excretion in the urine (cases 9-29 and 6-29) at two hour intervals following abrupt withdrawal of the drug for thirty hours. The total amount of morphine given twenty-four hours prior to withdrawal was 30 grains (1.944 Gm.). The last single dose was 5 grains (0.324 Gm.).

one-fourth grain, and then an hourly average of about a thirtieth of a grain during the rest of the experiment. During withdrawal, the patient in case 6-29 eliminated about 0.040 Gm. the first four hours or a little less than two thirds of a grain, one-fourth grain for the next four hours, and an hourly average of a fortieth of a grain for the rest of the experiment. Both addicts had been receiving 5 grains every four hours and, each time the administration was due, showed the usual eagerness for the drug. When the interval was lengthened to eight hours, restlessness manifested itself and a dosage of one-fourth grain given at this time had little effect. These curves, we think, show clearly a relationship between the rapidity of excretion of morphine and the desire for the next dose. As the total amount of drug in the body falls to a certain level, indicated by the change of rate of excretion about

the fifth hour, the patient shows an eagerness for the drug. If no drug is given at this time and that present in the body is further depleted, symptoms of withdrawal soon become evident.

Chart 2 contains the record of the temperature of the patient with pneumonia (case 11-29), as well as of the elimination of morphine during the various arbitrary periods and the total nitrogen during these same periods. Throughout the entire course of the disease and convalescence, he received 15 grains every twenty-four hour period. It will be noted that during the first three days of fever the patient eliminated in the urine 13.3 per cent of the total morphine given. Following the first three days of the fever the patient became desperately ill, and con-

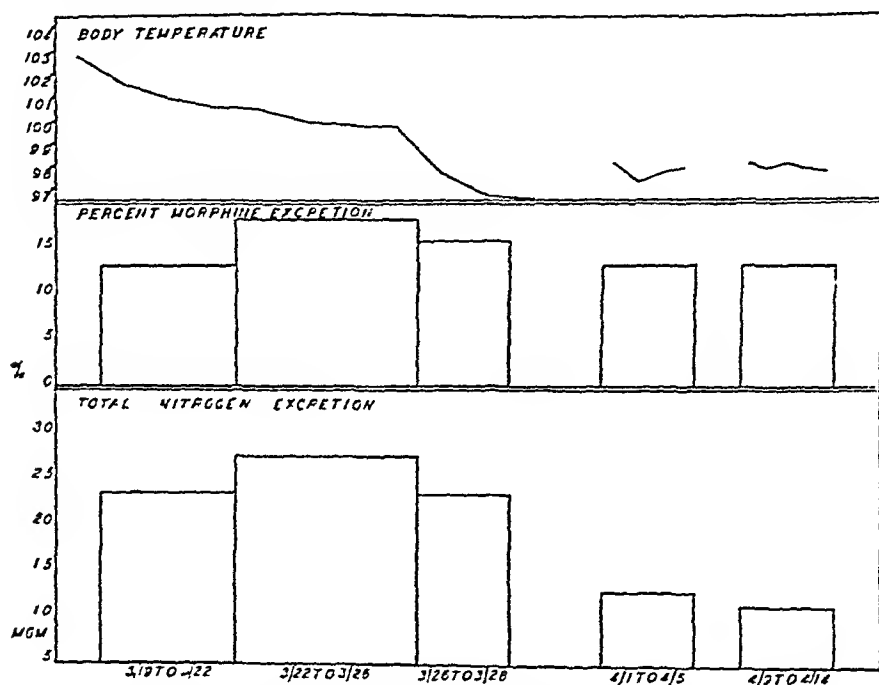


Chart 2—Curve showing the bodily temperature and the excretion of morphine and total nitrogen in the urine per twenty-four hour period during the illness and convalescence of a human addict suffering with pneumonia. Fifteen grains of morphine was administered daily throughout the disease and convalescence.

tinued so for four days, during this time the elimination of morphine in the urine was 18.2 per cent of the amount administered. The crisis now ensued and during the following forty-eight hours only 15.7 per cent of the morphine appeared in the urine. A week later, during what we term the convalescent period, 13 per cent of the morphine given was recovered, and two weeks after the crisis the amount eliminated was still the same.

It is during the period just preceding the crisis in pneumonia that the various organs began to show cloudy swelling and degenerative processes, the urine in this case, however, remained remarkably free



from albumin. During this period the total excretion of nitrogen as well as the elimination of morphine rose. This relationship is striking. Increased elimination of nitrogen indicates a break-down of the tissues, while increased elimination of morphine probably indicates a decreased capacity for retaining or destroying the drug. Hence, as those tissues which normally retain or destroy morphine begin to degenerate, the kidneys eliminate the excess drug.

The prompt recovery of the addict while receiving the 15 grains daily throughout the period of illness and convalescence supports the belief in the harmlessness of the drug on organic functions when the body is accustomed to it. This statement may be challenged in this particular case and the question may be raised whether the patient might not have been less ill had he not been given the drug. However, realizing that withholding the drug from an addict always results in the appearance of symptoms of withdrawal and not wishing to add to the patient's suffering, we felt justified in continuing the drug to avoid the discomfort of withdrawal.

The general condition of the healthy addicts under these various dosages is of interest. It was not a difficult procedure to increase the dosage from 10 (0.648 Gm.) to 60 grains daily within two or three days. Practically all our patients showed a gain in weight in the hospital while receiving these various amounts. No symptoms of intoxication appeared during the administration of the large quantities. One patient showed a tendency to slight drowsiness when left absolutely alone, but any interesting event or conversation resulted in his immediate attention and participation. Sudden reduction from 60 to 30 grains resulted in a marked change of disposition, this was more marked in abrupt reduction from 30 to 15 grains, and was even worse in reduction from 15 to  $7\frac{1}{2}$  grains (0.486 Gm.). All patients subjected to this drastic reduction manifested marked changes in disposition. No symptoms of withdrawal were evident, except slight relief from constipation. The patients complained bitterly during this abrupt reduction, but we are convinced that this would have been avoided had not a certain familiarity developed between the patients and the observers during the progress of the experiment.

#### CONCLUSIONS

Quantitative estimation of the elimination of morphine in the urine of human addicts showed a remarkable constancy in ratio to the amounts administered. The daily administration of 15, 30 and 60 grains resulted in an average elimination of 87, 98 and 107 per cent, respectively. The length of addiction, quantities taken just prior to admission, age, weight and volume of urine did not influence this rate.

Fecal excretion of morphine fell far below the urinary level, but was too variable to justify general conclusions

Abrupt withdrawal of morphine resulted in a rapid fall in urinary excretion during the first four hours, followed by a much lower and constant level for the next twenty-six hours

The elimination of morphine in an addict suffering with lobar pneumonia, to whom 15 grains was administered daily throughout the illness and convalescence, showed the same level of excretion during the early part of the disease, following the crisis and during the convalescent period, but a rise in the period just before the crisis when he was critically ill. No unusual signs or symptoms appeared during the illness that could be attributed to the morphine

# OPIUM ADDICTION

## XI GENERAL SUMMARY \*

ARTHUR B LIGHT, M D

<sup>2</sup> PHILADELPHIA

The narcotic problem is recognized today as one of the most important medical and sociologic problems confronting the medical profession. Although isolated studies on the problem have been made from time to time, no comprehensive investigation of its aspects, biologic, medical, social, economic and legal, has been consistently pursued until recent years. The Committee on Drug Addiction in affiliation with the Bureau of Social Hygiene, Inc., of New York has been engaged since 1921 in the study of this important problem. An extensive compilation of facts known and of views held with respect to opium addiction was made by Terry and Pellens <sup>1</sup> and published by the committee in book form. These inquiries demonstrated an urgent need for further investigation of the various phases of the problem by careful scientific methods, and accordingly the committee subsidized a number of field studies, experimentation in several university laboratories and a clinical study of the addict in the wards of the Philadelphia General Hospital.

The results of this clinical study have been published in a series of papers of which this is a brief summary.

The study was designed to determine whether objective investigations would reveal any changes that can be measured by physical, chemical or physiologic methods in the addict who is taking daily doses of from  $\frac{1}{2}$  to 60 grains (0.032 to 3.94 Gm.) of heroin or morphine that would differentiate him from a normal person, would serve to identify the state of opium addiction or would provide indications to guide in his rehabilitation.

It aimed furthermore to study by similar methods the addict during the period immediately after withdrawal of the drug at the time when he is suffering from "withdrawal symptoms." This characteristic train

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<sup>2</sup> From the Narcotic Wards of the Philadelphia General Hospital

Expenses of this research were defrayed by the Committee on Drug Addictions, New York City, and this work was carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction, in the wards of the Philadelphia General Hospital, which were placed at my disposal through the courtesy of the Director of Public Health, City of Philadelphia.

1 Terry, Charles E., and Pellens, Mildred. The Opium Problem, Camden, N. J., Haddon Craftsmen, 1925

of symptoms consists, in about the following order, of yawning, lachrymation, sneezing, restlessness, sweating, hot flashes and chills, vomiting, diarrhea, cramps in the extremities and abdomen, muscular tremors, marked irritability, complaints of extreme weakness, loss of weight, marked pilomotor activity, rarely diplopia and occasionally death. These symptoms reach their height at the end of about seventy-two hours following the withdrawal of the drug, and with the exception of occasional complaints of weakness, gradually subside in from five days to two weeks. Readministration of morphine in the amounts usually taken or in smaller amounts will within from five to thirty minutes bring about complete relief from all these symptoms. The addict professes to feel normal again with regained strength.

After successful withdrawal when the drug has been withheld for from ten days to two weeks the addict is taking food normally, has regained his weight and presents the picture of well being. If he should now revert to the drug, he will never start with more than  $\frac{1}{8}$  or  $\frac{1}{4}$  gram (0.008 or 0.016 Gm.) of heroin or morphine, larger amounts than this causing toxic symptoms and even death. The addict is again for the time being similar to normal persons in respect to tolerance. A group of addicts at this period was studied by the same methods to detect any difference in them when their tolerance had disappeared.

Finally a study was made in collaboration with the Department of Pharmacology of the University of Pennsylvania on the excretion of morphine in the addict.

Our general method of approach in these studies has been as follows. A suitable addict having been selected on admission, his dosage of morphine was for a time continued hypodermatically in sufficient quantities to prevent the appearance of withdrawal symptoms. During this period of several days he was measured, weighed, his vital capacity was determined and he was allowed to remain about the ward. A standard series of studies was then carried out and designated as "during the addiction period." The drug was then abruptly withdrawn for forty-eight hours, the patient being carefully watched and observed during this period. At the end of this time, the same series of studies was again made. He was now given sufficient morphine to bring about complete relief. Again the same studies were carried out. Within a day or two the hyoscine method of treatment was employed, and at the end of about ten days when the patient was ready for discharge from the hospital and said that he was feeling well, the series of studies was again carried out.

Our investigations were readily made during addiction and following treatment but met with many failures during withdrawal, as the patients often refused to cooperate. In the first paper of the series, we have

described the type of addict with which we have dealt and have pointed out some of the precautions which must be observed to avoid being deceived by the addict's tricks to obtain drug and by his tendency to simulate a state of either suffering or of well being as may best serve his purposes

#### RESULTS OF STUDIES

The results may be summarized as follows

In a series of opium addicts who were given morphine in sufficient quantities to prevent withdrawal symptoms, a study of the pulse rate and blood pressure while the subjects were standing and again while they were reclining, of the respiration, electrocardiograms and the response to staircase climbing tests, resulted in the finding of no marked deviation in the behavior of the circulation and respiration from that of normal persons

In 70 per cent of the cases the average pulse rate while the subject was reclining was slightly below the usual average figures given for normal persons

Orthodiagrammatic measurements showed a tendency to a smaller size for the heart than the average for normal persons <sup>2</sup>

A series of addicts receiving morphine sulphate hypodermatically has been studied with respect to the following hemoglobin, red blood cell count, white blood cell count, differential count, sedimentation rate, blood viscosity, cell volume, Wassermann reaction, specific gravity of the blood and plasma, plasma refractive index, dry matter of the blood and plasma, plasma  $p_H$ , carbon dioxide capacity of the plasma, serum conductivity, sugar, urea, creatinine, uric acid, cholesterol, chloride and lactic acid of the blood and calcium, magnesium and phosphate of the serum

In a general way there was a tendency for low red count, and high leukocyte count, but not uniformly in all cases. The cholesterol was usually increased and the phosphate diminished. The lactic acid was uniformly high. No other constituents showed any suggestive departure from the normal.

A slight degree of anemia may be present when the addict is forced to live in poor hygienic surroundings when all his funds are required to purchase the drug at the expense of sufficient nourishing foods <sup>3</sup>

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2 Light, Arthur B, and Torrance, Edward G. Opium Addiction. III. The Circulation and Respiration of Human Addicts During the Administration of Morphine, Arch Int Med **43** 556 (April) 1929

3 Karr, Walter G, Light, Arthur B, and Torrance, Edward G. Opium Addiction. IV. The Blood of the Human Addict During the Administration of Morphine, Arch Int Med **43** 684 (May) 1929

Studies of the stomach, kidney, liver, basal metabolism, thymus, temperature, dextrose response to epinephrine and to morphine revealed no fundamental differences in addicts who were administered morphine to supply their needs, except a slight delay in the average response of gastric secretion to a test meal, the presence of albumin in the urine in 17 per cent of the cases and wide fluctuations of the individual determinations of basal metabolism but an average metabolism within the normal limits. A delay in the return to normal of the blood sugar following the ingestion of dextrose by mouth was also noted <sup>4</sup>

We have been unable to detect any marked physical deterioration or impairment of physical fitness aside from the addiction per se in the series of cases of opium addiction studied during the administration of morphine.

The existence of considerable emaciation in certain cases we believe to be caused by the unhygienic and impoverished life of the addict rather than by the direct effects of the drug <sup>5</sup>

Abrupt withdrawal of morphine for twenty-four hours in four addicts resulted in the appearance of mild withdrawal symptoms. These symptoms were accompanied with slight negligible changes in the pulse rate, leukocyte count and basal metabolism rate. Changes in behavior and irritability would indicate that mental suffering begins before physical suffering.

Abrupt withdrawal of morphine for forty-eight hours from a series of ten addicts resulted in the appearance of rather severe withdrawal symptoms. One addict showed diplopia. These changes were accompanied by a definite leukocytosis in eight of the ten cases, concentration of the blood in all cases and a slight rise in cholesterol of the blood in seven. Albuminuria was found in two cases. The  $p_H$  of the blood, urea nitrogen and sugar showed no changes. Considerable loss of weight was found during the forty-eight hour withdrawal period.

Following the readministration of the drug and relief from subjective symptoms, the increased leukocyte count and concentration of the blood still remained, as did the diplopia and muscular twitchings of the face, for several hours. A rise in the percentage saturation of the oxygen of venous blood was noted in all cases following the readministration of the morphine. The circulatory changes noted were a slight increase in the pulse rate and a slight fall in systolic pressure. Staircase

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4 Light, Arthur B., and Torrance, Edward G. *Opium Addiction*. V Miscellaneous Observations on Human Addicts During the Administration of Morphine, *Arch Int Med* **43** 878 (June) 1929.

5 Light, Arthur B., and Torrance, Edward G. *Opium Addiction*. II Physical Characteristics and Physical Fitness of Addicts During the Administration of Morphine, *Arch Int Med* **43** 326 (March) 1929.

climbing and Schneider's test showed a decrease in the efficiency of the circulation following the readministration of the drug when compared to the results obtained at the end of the forty-eight hour withdrawal period <sup>6</sup>

Abrupt withdrawal of morphine in a series of human opium addicts resulted in a negative water balance, and in two of these subjects in increased elimination of uric acid. The negative water balance is most likely due to failure to take sufficient food and water although increased loss of water from increased metabolism cannot be entirely excluded, particularly in view of the restlessness of these subjects during withdrawal.

While taking their first year final examinations, three medical students used as control subjects failed to show a negative water balance, any increase in frequency of urination or increased twenty-four hour output, and retained their weights, on the days of the final examinations <sup>7</sup>

Studies of a series of opium addicts before and after treatment with scopolamine resulted in the following positive changes: loss of weight, slight rise in temperature, appearance of albuminuria, slight leukocytosis, slight concentration of the blood, a rise in the  $p_H$  of the blood, a rise in the lactic acid of the blood, a fall in the carbon dioxide capacity and a fall in the total number of points scored with Schneider's test of physical fitness.

No significant changes were found in a comparison of the pulse, respiration rates and blood pressure while the addict was reclining, heart measurements, electrocardiographic studies, staircase climbing tests, effect of atropine sulphate on the P-R interval, vital capacities, blood urea nitrogen, blood sugar, blood uric acid, blood cholesterol, whole blood chloride, serum calcium and phosphate, blood viscosity, sedimentation tests, basal metabolism, phenolsulphonphthalein tests, phenoltetrachlorophthalein test of liver function, icterus index, van den Bergh's tests and blood sugar response to epinephrine.

The few positive observations do not coincide with the general appearance and behavior of the addict. He may present some or all of the foregoing positive observations and yet appear and behave as though he were normal. On the other hand, he may give the appear-

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6 Light, Arthur B., and Torrance, Edward G. Opium Addiction VI The Effects of Abrupt Withdrawal Followed by Readministration of Morphine in Human Addicts, with Special Reference to the Composition of the Blood, the Circulation and the Metabolism, *Arch Int Med* **44** 1 (July) 1929.

7 Light, Arthur B., and Torrance, Edward G. Opium Addiction IX Water Balance Studies During the Administration and Withdrawal of Morphine *Arch Int Med* **44** 693 (Nov) 1929.

ance of one who is quite ill and yet not show any of the foregoing positive observations<sup>8</sup>

The effect of intramuscular and intravenous administration of large doses of morphine was tested on five addicts, one of whom was at times accustomed to the intravenous administration of the drug, while the other four, accustomed to the hypodermatic method, volunteered as subjects for this study

The intramuscular injection of morphine sulphate in dosages of three, four and six times the usual amounts given, and the intravenous injection of dosages six, seven and nine times the amounts usually given to the human opium addicts who acted as subjects resulted in insignificant changes in the pulse and respiration rates, electrocardiogram, chemical studies of the blood and the behavior of the addict

The intravenous administration of 20 and 11 grains (1.3 and 0.715 Gm) to two addicts following a forty-eight hour withdrawal period in fifty-six minutes and one hour and sixteen minutes, respectively, also failed to produce any significant physiologic changes or changes in behavior

Analyses of the blood for morphine showed the presence of less than 1 mg per twenty-five cubic centimeters of blood, indicating its rapid removal following the completion of the injection<sup>9</sup>

In a series of addicts it has been possible to control reliably the morphine dosage, to vary this at will and to collect the excreta quantitatively

Quantitative estimation of the elimination of morphine in the urine of human addicts showed a remarkable constancy in ratio to the amounts administered. Daily administration of 15 (0.972 Gm), 30 (1.944 Gm) and 60 grains (3.888 Gm) resulted in an average percentage elimination of 87, 98 and 107, respectively. The length of addiction, quantities taken just prior to admission, age, weight and urine volume did not influence this rate.

Fecal excretion of morphine fell far below the urinary level, but was too variable to justify general conclusions.

Abrupt withdrawal of morphine resulted in a rapid fall in urinary excretion during the first four hours followed by a much lower and constant level for the next twenty-six hours.

The elimination of morphine in an addict suffering with lobar pneumonia, to whom a daily administration of 15 grains (0.972 Gm) was

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8 Light, Arthur B., and Torrance, Edward G. *Opium Addiction VII A Comprehensive Study of the Effects of the Scopolamine Treatment for Morphine Addiction*, Arch Int Med **44** 194 (Aug) 1929

9 Light, Arthur B., and Torrance, Edward G. *Opium Addiction VIII The Effects of Intramuscular and Intravenous Administration of Large Doses of Morphine to Human Addicts*, Arch Int Med **44** 376 (Sept) 1929



maintained throughout the illness and convalescence, showed the same level of excretion during the early part of the disease, following the crisis and during the convalescent period, but a rise in the period just before the crisis when the patient was critically ill. No unusual signs or symptoms appeared during the illness that could be attributed to the morphine<sup>10</sup>

#### COMMENT

These results are of definite importance. The study shows that morphine addiction is not characterized by physical deterioration or impairment of physical fitness aside from the addiction per se. There is no evidence of change in the circulatory, hepatic, renal or endocrine functions. When it is considered that these subjects had been addicted for at least five years, some of them for as long as twenty years, these negative observations are highly significant. The study offers substantial grounds for the belief that were it possible to relieve the addict of his addiction complete rehabilitation could be expected.

The abrupt withdrawal of morphine was accompanied by only slight changes in the physiologic mechanisms studied, changes which afforded no adequate explanation of the withdrawal symptoms.

The readministration of morphine during the period of the withdrawal symptoms was not accompanied by return to normal of those few positive observations characteristic of the withdrawal period in spite of the apparent return of the addicts to a sense of well being. Schneider's test of physical fitness and the staircase climbing test indicated a poorer response than during the period of suffering.

Following treatment and just before discharge from the hospital, our studies again indicate few changes except that the average leukocyte count was still high, a slight concentration of the blood still persisted, a slight rise in the average for the  $p_H$  and lactic acid of the plasma and a decided fall in the efficiency tests were found. One cannot correlate these observations with the behavior of the patients.

The study appears to us to be conclusive with respect to the physiologic reactions of the addict which we investigated. It indicates, however, the necessity for a study of the addict from some new standpoint in order to reveal the factors which induce and maintain the state of addiction and which on abrupt withdrawal of the drug elicit the withdrawal symptoms.

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10 Fry, Edith G., Light, Arthur B., Torrance, Edward G., and Wolff, William A. Opium Addiction. X. Excretion of Morphine by Human Addicts, *Arch Int Med*, this issue, p. 862.

# BLOOD PRESSURE AND WEIGHT\*

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The study of large groups of persons seems to establish a definite relationship between the weight of the body and the arterial blood pressure. Faber,<sup>1</sup> in his report of 1,000 approximately normal children between the ages of 4 and 16 years, showed a striking and corresponding rise in both systolic and diastolic blood pressure with a rise in body weight in each group. Since arteriosclerosis and other diseases which predispose to arterial hypertension may be excluded in these persons, the evidence of the relationship of body weight to blood pressure appears even more conclusive. That deviation from the normal body weight is associated with definite variation in blood pressure in otherwise normal persons is well demonstrated by Symonds.<sup>2</sup> His review of the results of 150,419 examinations for life insurance revealed steplike variations in the blood pressure between the various groups. There was a fall in both systolic and diastolic pressure in each group in which the subjects were below normal body weight, and a corresponding rise in blood pressure in each group made up of persons who were above normal body weight.

The significance of the type of body build as related to blood pressure is pointed out by Larimore.<sup>3</sup> His studies of factory workers, of whom 177 were males and 237 females, show that persons of the sthenic type have definitely higher systolic and diastolic blood pressures than those who are of the asthenic type. In persons of the intermediary, hyposthenic type, the averages for blood pressure were between the averages for the sthenic and the asthenic groups. Faber<sup>4</sup> tended to corroborate this observation in his conclusion that in men of equal weight the blood pressure is slightly lower in those of greater height.

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\* Submitted for publication, May 28, 1929.

<sup>1</sup> From the Medical Division of the Mayo Clinic and the Mayo Foundation.

<sup>1</sup> Faber, H. K. A Formula Expressing a General Relationship Between Pressure and Body Weight, *Proc Soc Exper Biol & Med* **25** 77, 1927.

<sup>2</sup> Symonds, Brandreth. The Blood Pressure of Healthy Men and Women, *J A M A* **80** 232 (Jan 27) 1923.

<sup>3</sup> Larimore, J. W. A Study of Blood Pressure in Relation to Types of Bodily Habitus, *Arch Int Med* **31** 567 (April) 1923.

<sup>4</sup> Faber, quoted by McWilliam, J. A. Blood Pressure in Man, Normal and Pathological, *Physiol Rev* **5** 303, 1925.

The relation between arterial hypertension and groups of persons above normal body weight is pointed out by Huber,<sup>5</sup> who cited evidence obtained from the examination, in 1923, of 12,000 army officers. Furthermore, in his own study of the results of 1,332 examinations made in the army, he found that 18 per cent of those who were overweight had arterial hypertension (systolic), only 15 per cent of those of normal weight and 11 per cent of those who were underweight exhibited arterial hypertension (systolic). More striking evidence of this relationship is reported by Terry,<sup>6</sup> in whose series of sixty-three obese patients, thirty-seven (58 per cent) were found to have arterial hypertension, or average blood pressures of 173 systolic and 96 diastolic for the entire hypertensive group. Twenty-four of these obese patients were placed on a dietary regimen, and after an average loss of 12 pounds (5.4 Kg.), the average arterial blood pressure for the group of twenty-four fell from 196 systolic and 103 diastolic to 170 systolic and 95 diastolic. Similar results were reported by Rose<sup>7</sup> in his series of ten obese patients whose weights were reduced by a dietary regimen.

It has been shown<sup>8</sup> that in patients suffering from cholecystitis the blood pressure curve, when corrected for body weight, was lowered so that it varied little from the accepted curve for normal blood pressure and so that it correlated with that of patients with gastric ulcer. Moreover, the blood pressure curve in gastric ulcer was raised when a correction for weight was made. Since the body weight in cholecystitis frequently is above normal and that in gastric ulcer frequently is below normal, the value of correcting blood pressure for body weight seems evident.

#### PRESENT STUDY

A study has been undertaken for the purpose of determining the relationship, if any, that exists between arterial blood pressure and body weight. In other words, an attempt has been made to determine whether the rule that blood pressure is increased in obese and lowered in emaciated persons holds in the physician's office, irrespective of the medical status of his patients. The attempt was not to establish normal values, but to find whether impressions gained from normal persons apply to all patients in a general clinical practice, and to determine how dominant

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5 Huber, E. G. Systolic Blood Pressure of Healthy Adults in Relation to Body Weight, *J. A. M. A.* **88** 1554 (May 14) 1927.

6 Terry, A. H., Jr. Obesity and Hypertension, *J. A. M. A.* **81** 1283 (Oct 13) 1923.

7 Rose, R. H. Weight Reduction and Its Remarkable Effect on High Blood Pressure, *New York M. J.* **115** 752, 1922.

8 Hartman, H. R., and Brown, G. E. A Statistical Study of the Systolic Blood Pressure in Cases of Duodenal and Gastric Ulcer, this issue, p. 843.

is the factor of weight in influencing blood pressure. Many of the persons studied were in a normal state of health.

To obtain the data for this study, records of 2,042 consecutive registrants, aged 15 or more, were taken from the file of the Mayo Clinic for June, 1927. Nine hundred and fifty-nine of the subjects were males and 1,083 females.

By use of the Nylic Standard Table of Heights and Weights compiled by Dr. Oscar H. Rogers of the New York Life Insurance Company, percentage deviation from normal weight was computed in each case. Arrangement of groups by percentage deviation from normal was then accomplished for males and for females. Those persons within 10 per cent above or below the accepted normal were grouped as "normal." The grouping utilized was as follows:

- Group 1—26 to 50 per cent underweight
- Group 2—11 to 25 per cent underweight
- Group 3—Normal weight
- Group 4—11 to 25 per cent overweight
- Group 5—26 to 50 per cent overweight
- Group 6—51 to 75 per cent overweight
- Total underweight
- Total overweight

The mean blood pressures within each group subsequently were utilized to compute the systolic and diastolic blood pressures for each designated group. The probable errors of the differences were computed<sup>9</sup> to ascertain the significance of the variation between the blood pressures of the groups.

The average blood pressures for the groups, with the designation of the probable error, were then plotted graphically (charts 1 and 2). The minus probable error is shown in the charts.

#### COMMENT

Chart 1 shows in males an almost steplike rise from group 1 to group 6 in the mean values for the systolic blood pressures of the groups. Here the most significant rise of systolic blood pressure is demonstrable between groups 3 and 4. The marked difference between the total underweight (125.1 systolic) and the total overweight (141.2 systolic) male groups is strikingly significant, with odds of sixty-five billion to one given to this difference.<sup>10</sup>

<sup>9</sup> Rugg, H. O. *Statistical Methods Applied to Education*, Boston, Houghton Mifflin Company, 1917, pp. 410.

<sup>10</sup> Pearl, Raymond. *Medical Biometry and Statistics*, Philadelphia, W. B. Saunders Company, 1923, p. 209.

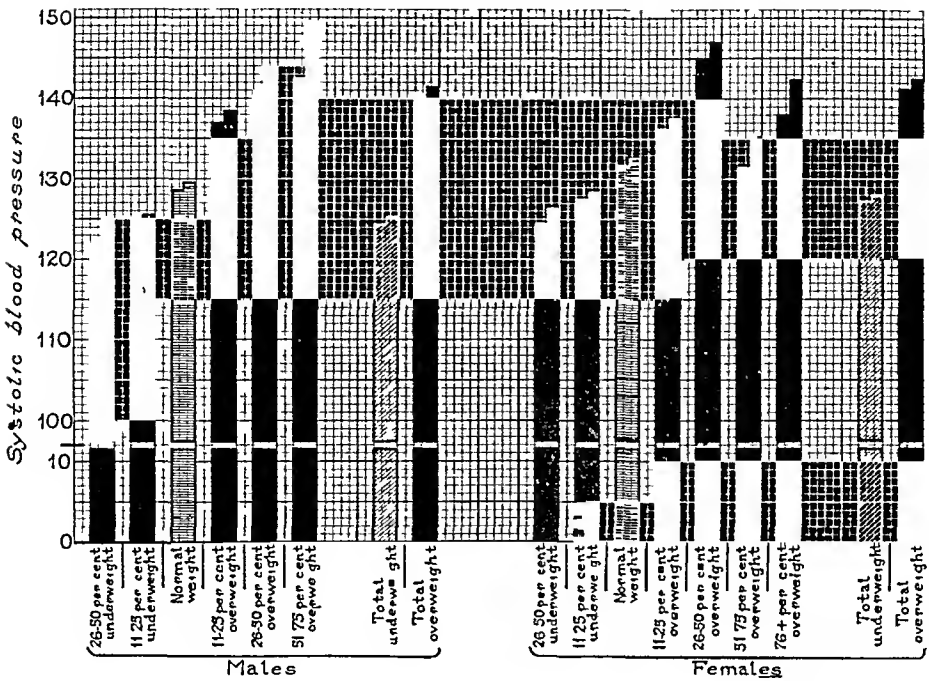


Chart 1—Graphic representation of average systolic blood pressure in underweight and in overweight males and females, all ages. The plotted length of notches indicates the probable error. The horizontal white strip in this and the following chart indicates that the plot of blood pressure from 10 to 100 is omitted to save space.

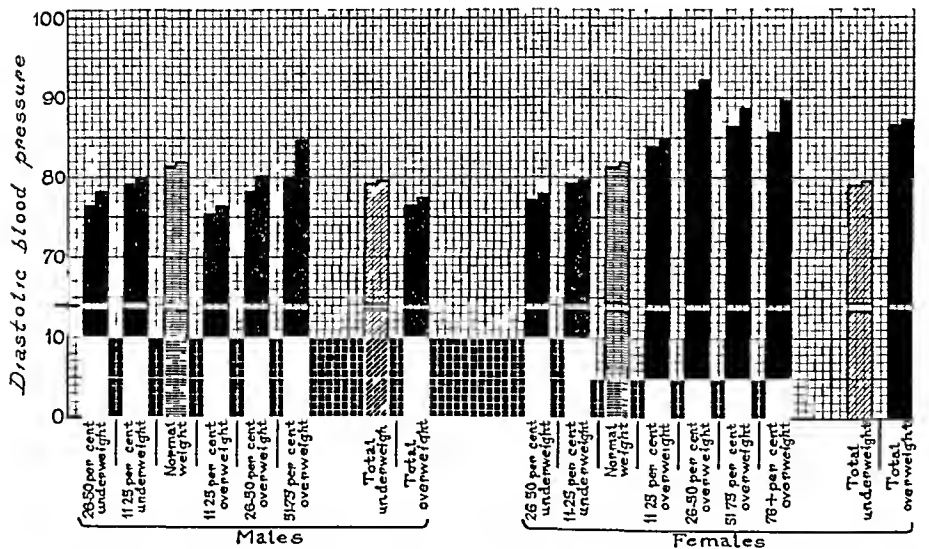


Chart 2—Graphic representation of average diastolic blood pressure in underweight and in overweight males and females, all ages.

In the females there is a similar steplike rise in the systolic blood pressure, with increase in body weight until groups 5 and 6 are reached, where there is a fall from the peak (146.7 systolic). The small number of cases (eighteen and four, respectively) in these last groups allows this apparent discrepancy, but there is little or no significance in view of the large probable errors involved. The marked difference between the total underweight (127.8 systolic) and total overweight (142.2 systolic) female groups is practically as striking and is equally as significant as it is in the males.

In chart 2 it is shown that the means for diastolic pressures and the body weight were correlated in females only, and the differences between the classes according to weight, of course, were small. In the males the mean value for diastolic blood pressure in the total overweight group was even smaller than that in the total underweight group, and the means in the different groups according to weight were not consistent with the corresponding systolic averages. The small weight of significance given these diastolic variations allows for a possibility that a larger group study might reveal the expected steplike rise in males, as is found more significantly in females. The averages for diastolic pressure in the female group proved consistent with the corresponding systolic averages throughout.

This lack of constancy in diastolic blood pressure could be traced readily to lack of uniformity of technic in taking the readings. The phenomena on which the record of diastolic blood pressure is based are not as sharply defined as are those of the systolic pressure. All readings were taken by a trained but diversified group of clinicians who used a spring sphygmomanometer which every seven days was checked against a mercury sphygmomanometer. The inconstancy of the diastolic readings emphasizes only the striking constancy of increase of systolic blood pressure with increasing weight in a nonselected group of office patients in a general clinical practice. Weight must be a dominant factor in determining systolic blood pressure. Lack of correlation in the males, lack of uniformity of technic and instability of diastolic blood pressure itself preclude logical relationship being drawn between diastolic blood pressure and body weight in this particular study.

# HEMOCHROMATOSIS IN A METAL WORKER

CASE REPORT WITH AUTOPSY AND A BRIEF REVIEW OF THE  
LITERATURE \*

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AND

T FITZ-HUGH, JR, MD

PHILADELPHIA

The classic picture of "diabète bronze" is rarely seen in this clinic, in spite of the belief of Mallory<sup>1</sup> that its fundamental pathologic background is not uncommon. Our interest was keen, therefore, when a man was admitted to the ward, not only presenting this condition in characteristic form, but also giving the remarkably apopos history that he had been a metal worker, in brass, steel and copper, for more than twenty years.

With the diagnosis practically "ready made" at the outset, we were able to plan and carry out fairly complete clinical and laboratory studies, which, together with autopsy observations, form the basis of this report.

Our purpose was (1) to search for evidence of copper poisoning in relation to hemochromatosis, (2) to observe the effectiveness or non-effectiveness of insulin in controlling carbohydrate disturbances in a pancreatic disease known to be progressive and further complicated by liver disease, and (3) to study by clinical and laboratory methods the other endocrine glands which might be affected in this remarkable condition. When death ensued in spite of our best efforts, the autopsy enabled us to correlate the clinical and pathologic observations.

## REPORT OF CASE

*History*—J M, a white man, aged 48, married, was admitted to the University of Pennsylvania Hospital to the service of Dr Alfred Stengel on Dec 21, 1927. Two years previously when he was apparently well he began to experience gnawing epigastric pain, three hours after meals, which was relieved by food and sodium bicarbonate. He had never been free from this pain for more than a week since its onset. About a year before, his friends noticed that the skin of his hands, forearms and face was becoming darker. This coloring progressed gradually until

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\* Submitted for publication, June 20, 1929.

<sup>1</sup> From the Medical Division Hospital of the University of Pennsylvania.

1 Mallory, F B, Parker, F, Jr, and Nye, R N. Experimental Pigment Cirrhosis Due to Copper, and Its Relation to Hemochromatosis, *J M Research* **42** 461, 1921. Mallory, F B. Hemochromatosis and Chronic Poisoning with Copper, *Arch Int Med* **37** 336 (March) 1926, Relation of Chronic Poisoning with Copper to Hemochromatosis, *Am J Path* **1** 117, 1925.

his admission to the hospital. About two months before admission he began to exhibit loss of weight, polydipsia and polyuria. Sugar was found in the urine at this time, although two previous examinations during the past year had been negative in this respect. He had blurring of vision, dyspnea and palpitation on exertion, weakness, loss of libido and some numbness and tingling of the fingertips for the past two months.

He had had an umbilical hernia for two years, small hemorrhoids for ten years and multiple subcutaneous tumors for twenty years. He said that he had never had venereal disease.

His family history indicated nothing of importance except that he had four healthy children, and that his mother had similar multiple tumors beneath the skin.

He had worked in a machine shop for twenty years, usually with steel, often with brass and rarely with copper. During the grinding of these metals, he would become covered with the dust produced which would "work into his clothes," so that his underwear was thoroughly impregnated with it. He gave up this work three months before admission. His alcoholic habits were temperate. He took no silver preparations in any form.

*Physical Examination*—On admission to the hospital, the temperature and pulse rate were normal, the blood pressure was 112 systolic and 68 diastolic. He was emaciated. The skin of the hands, forearms, face and neck was dry, scaly and of a striking dusky leaden hue. This pigmentation was less noticeable in those parts of the body covered by clothing. His face was feminine in configuration, with "retrousse" nose and pointed chin. His voice was feminine in tone. He had no axillary or thoracic hair, and the pubic hair was scanty and feminine in distribution. The mouth showed poor dental hygiene but no abnormal mucosal pigmentations. The heart and lungs were normal. Abdominal examination revealed a small umbilical hernia and a large, hard, bulging liver, extending down to within 1 cm. of the umbilicus. This organ showed relatively more enlargement of the left than of the right lobe so that its edge made a nearly horizontal line across the abdomen. The spleen was indefinitely palpable. On auscultation a peculiar humming sound was heard to the left of the umbilicus, not unlike the sound of wind blowing through telephone wires. It grew louder during cardiac systole and faded in diastole. It ceased entirely when moderately firm pressure was made with the stethoscope, or with the finger in the vicinity of the stethoscope. There was moderate ascites. The genitalia were grossly normal. There was general adenopathy of a mild degree. The multiple subcutaneous, circumscribed, fairly soft, almost symmetrical tumors, not more than fifteen in all, previously mentioned, were noticed in the various parts of the body, but chiefly on the extremities.

The diagnosis of hemochromatosis was made on the basis of this classic picture—a man in midlife with hepatic cirrhosis, diabetes mellitus and pigmentation. An additional unrelated diagnosis of familial lipomatosis completed our view of the case at this time. Abdominal neoplasm and Addison's disease were considered, but were ruled out.

*Laboratory Studies*—The urine throughout showed sugar. Ketone bodies were present on admission, and appeared now and then during his stay in the hospital. There were neither casts nor albumin. Urobilin was strongly positive, and there was a trace of bilirubin at times. Rous' modification of the Perl test<sup>2</sup> for hemosiderin in the urine was negative on three occasions, except for the finding of a few blue extracellular particles. No hemosiderin granules were found in the

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<sup>2</sup> Rous, P. Urinary Siderosis, J. Exper. Med. 28: 645, 1918.



unstained sediment. The intake and output of fluid bore normal relations to each other, except when ascites began to increase.

On admission, the blood showed a normal red and white cell count, hemoglobin, 82 per cent, and a differential count of neutrophils, 70, lymphocytes, 22, large mononuclears and transitionals, 8. Toward the end a moderate secondary anemia developed. No peculiarities were noted in the (Wright's) stained smear, and malarial organisms were not found. No phagocytes were seen containing hemosiderin. The reticulated red blood cells were 0.8 per cent. The fragility test was normal, hemolysis began at 0.450 and was complete at 0.325 per cent. The bleed-

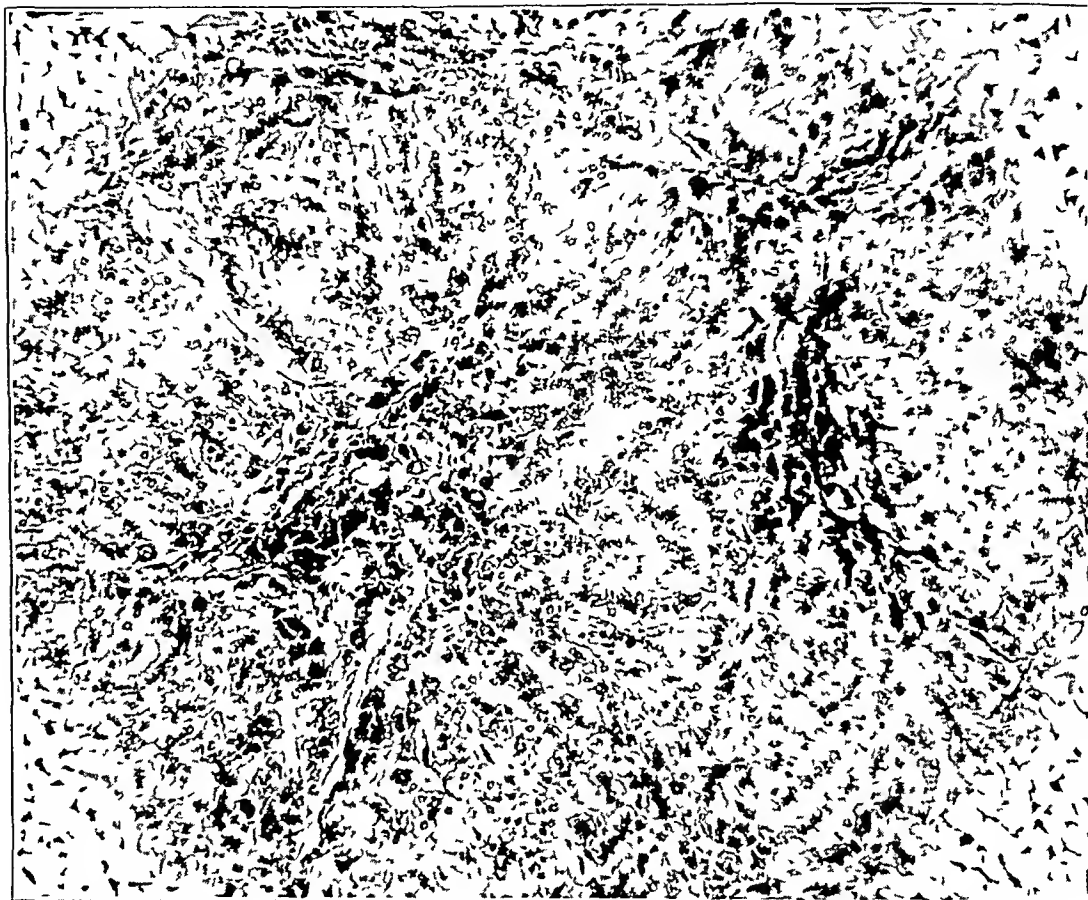


Fig 1—Section of the liver. Stained by Mallory's method (alum hematoxylin and ammonium sulphide). The hemosiderin granules take on an intense black color.

ing time was three minutes, and the tourniquet test was negative. The venous clotting time, clot retraction and blood fibrinogen were normal. The blood sugar varied from 0.145 to 0.280 per cent despite large doses of insulin daily (175 units) and a diet of protein, 75 Gm, fat, 125 Gm, and carbohydrate, 100 Gm. The blood carbon dioxide in mild acidosis was 42 per cent by volume and rose to 62 per cent by volume subsequently. The Wassermann reaction of the blood was negative. The van den Bergh test showed an indirect reaction of 1.3 and a negative direct reaction. The icterus index was unobtainable because of hemolysis which occurred on each of three occasions. The blood urea nitrogen was 9, 5, 8 and 12 mg per hundred cubic centimeters on various occasions.

The ascitic fluid obtained several times by paracentesis abdominis, was yellowish with a slight turbidity. The specific gravity was 1.008. There were 500 red and 52 white blood cells per cubic millimeter. Urea nitrogen and sugar were found in the same amounts that were present in the blood.

The basal metabolic rate was plus 2 per cent. Gastric analysis showed sustained high figures, the free hydrochloric acid being 72, the total hydrochloric acid, 88.

Roentgen studies gave the following results. The chest was normal. The pituitary fossa was slightly under the normal limits of size. Cholecystograms showed no shadow of the gallbladder in any of the films. Films of the gastro-

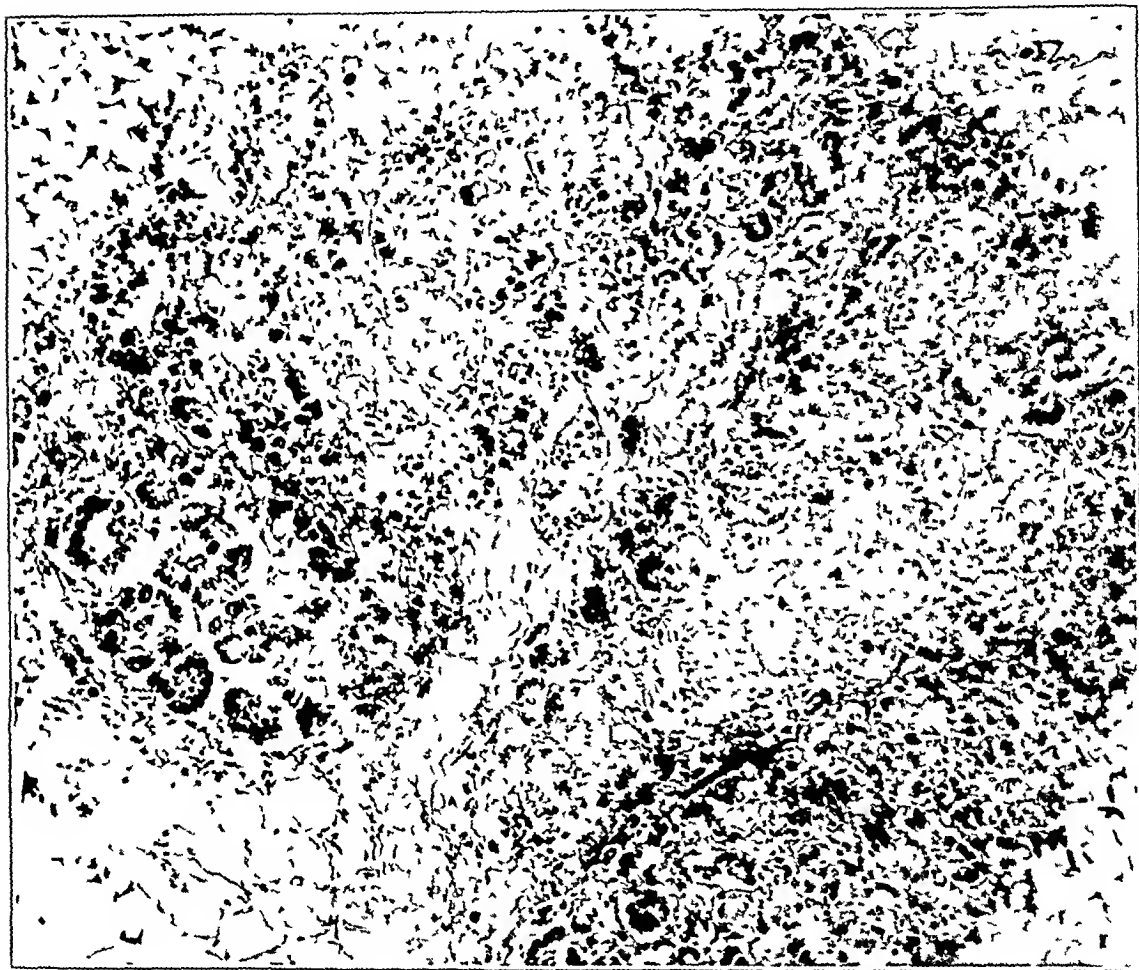


Fig. 2—Section of the pancreas. Same stain as in figure 1.

intestinal tract showed hyperperistalsis and hypermotility in the stomach, a constant duodenal cap deformity by the fluoroscope but not in the serial films, phrenopasm in the esophagus and hypermotility in the colon.

The visual fields and eye grounds presented nothing of importance. The electrocardiographic report was "rate 80, no arrhythmia recorded, P waves normal, P-R intervals 0.14 second, QRS complexes within normal limits, T-waves small in lead 1, inverted in lead 2. Tracing indicates marked functional depression of the myocardium, probably with myocardial disease."

A biopsy of the skin and of a lymph gland showed the presence of hemosiderin in considerable amounts in each. No copper was demonstrable. The subcutaneous tumors mentioned proved to be lipomas.

*Course*—The subsequent course was a steadily downward one characterized by persistently high blood sugar, recurrent ascites, progressive emaciation, diarrhea, abdominal pain, weakness, moderate anemia and edema of the lower extremities. The increased blood sugar did not yield to massive doses of insulin. On 175 units per day and a diet of protein, 75 Gm, fat, 120 Gm, and carbohydrate, 100 Gm, the blood sugar stayed consistently in the vicinity of 0.2 per cent. Increasing the insulin had little, if any, effect. Moreover, the patient showed evidence of insulin shock in only one rather doubtful instance.

Ten days after the last paracentesis abdominis, signs of peritonitis developed. This was attributed to a retrograde infection through the puncture wound, which

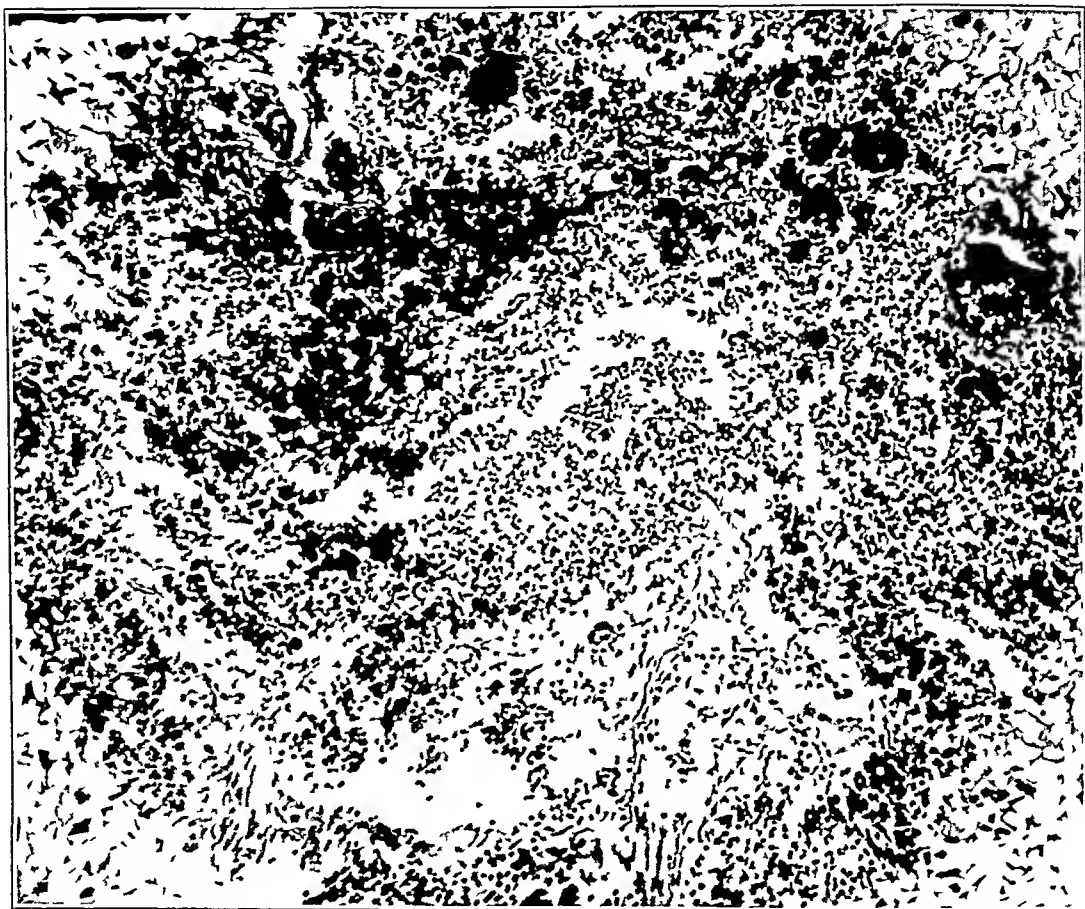


Fig 3—Section of a lymph node, near the pancreas. Same stain as in figure 1.

had continued to drain for several days. The patient had neither fever nor leukocytosis at any time. He died, in coma, of peritonitis on Jan 26, 1928, thirty-seven days after admission.

*Autopsy*—At autopsy the typical observations of hemochromatosis<sup>3</sup> were present: cirrhosis and marked hemosiderin pigmentation of the liver (fig 1), marked hemosiderosis of the pancreas (fig 2), the color being a deep chocolate brown, and a considerable hemosiderin deposit in the heart muscle and lymph

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3 Blanton, W. B., and Healy, W. Hemochromatosis. Report of Four Cases, *Arch Int Med* 27:406 (April) 1921.

glands, especially those in the retroperitoneal chains near the liver and pancreas (fig 3) No cause was found for the peculiar humming murmur to the left of the umbilicus, which was doubtless a venous bruit in the abdominal wall itself

The immediate cause of death was a condition which should have been diagnosed from the history and gastro-intestinal studies, namely, a ruptured duodenal ulcer The patient's typical history of ulcer was not appreciated correctly on account of the other upper abdominal pathologic changes When the signs and symptoms of



Fig 4—Photograph of the patient taken on Dec 27, 1928 The pigment is most noticeable on the face, forearms, hands, legs and feet

peritonitis developed, they followed uncomfortably closely on a paracentesis abdominis, so that the possibility of a ruptured ulcer was never suspected

#### COMMENT

Hemochromatosis is a disease characterized by (1) cirrhosis of the liver, (2) diabetes and (3) marked hemosiderin and hemofuscin deposits

in the various tissues, especially in the liver, pancreas, abdominal lymph nodes, exposed areas of the skin, heart muscle and endocrine glands Hanot and Chauffard <sup>4</sup> the earliest writers, believed that diabetes produced a generalized perversion of cellular metabolism. The hepatic changes incident to this widespread metabolic derangement resulted in interference with chromogenic function, and this in turn caused the pigment deposits. Von Recklinghausen <sup>5</sup> considered hemochromatosis as a "chronic form of hemorrhagic hepatitis" and a sign of a hemorrhagic diathesis. Rendu and de Massary <sup>6</sup> and Brault and Galliard <sup>7</sup> suggested that the cirrhosis of the liver was probably the primary etiologic factor. According to their opinion, pigment was deposited as a result of the extreme cachexia caused by the combination of diabetes and cirrhosis of the liver. Letulle, <sup>8</sup> P. Marie <sup>9</sup> and Jeanselme <sup>10</sup> believed that the pigment deposits came first, and that pancreatic and hepatic changes were secondary to it. They ascribed the hemosiderosis to an excessive blood destruction by some unknown toxin. Opie, <sup>11</sup> in 1899, likewise thought that the hemosiderin deposit preceded and caused the cirrhosis and the diabetes, but found no evidence of blood destruction or regeneration. He therefore suggested that some underlying hepatic dysfunction, with inability of the liver cells to effect the normal elaboration of bile pigments from the hemoglobin of the blood, might be responsible for the accumulation of hemosiderin in the tissues. Sprunt <sup>12</sup> agreed that pigment deposits appeared first, but invoked an intracellular metabolic

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4 Hanot and Chauffard. Cirrhose hypertrophique pigmentaire dans le diabete sucre, *Rev de med* **2** 385, 1882

5 Von Recklinghausen. Ueber Haemochromatose, *Tageblatt der 62te Versammlung deutscher Naturforscher und Aertze in Heidelberg*, 1889, p 324

6 Rendu and de Massary. Cirrhose et diabete bronze, *Bull et mem Soc med d hop de Paris* **14** 163, 1897

7 Brault, A, and Galliard, L. Sur un cas de cirrhose hypertrophique pigmentaire dans le diabete sucre, *Arch gen de med* **1** 38, 1888

8 Letulle. Cirrhose pigmentaire du foie, chez les diabetiques, *Semaine med* **5** 408, 1885

9 Marie, P. Sur un cas de diabete bronze suivi d'autopsie, *Semaine med* **15** 229, 1895

10 Jeanselme, M. E. Hematologie et pathogenie du diabete bronze, *Bull et mem Soc med de hop d Paris* **14** 179, 1897

11 Opie, E. L. A Case of Hemochromatosis. The Relation of Hemochromatosis. The Relation of Hemochromatosis to Bronzed Diabetes, *J Exper Med* **4** 279, 1899

12 Sprunt, T. P. Hemochromatosis. A Report of Three Cases and a Discussion of the Pathogenesis, *Arch Int Med* **8** 75 (July) 1911. Sprunt, T. P., Colwell, H. S., and Hagen, H. J. Pigment Formation in the Liver During Autolysis and Its Relation to the Pigmentation of Hemochromatosis, *J Exper Med* **16** 607, 1912

disorder of unknown origin as the cause of this separation of the "chromogenic groups of the proteid molecule" from the rest of the cell constituents

Gaskell and his co-workers,<sup>13</sup> McClure<sup>14</sup> and Howard and Stevens<sup>15</sup> studied cases of hemochromatosis with reference to undue retention of iron, but their work, although careful, was largely inconclusive. Other workers<sup>16</sup> had had similar experiences. Rous and his co-workers,<sup>17</sup> by repeated transfusions in rabbits, showed that hemosiderin deposits, simulating those in hemochromatosis, could be produced by the ensuing increased blood destruction. They admitted, however, that such an excess of hemolysis could not be the sole cause of the disease. Rous believed that cirrhosis of the liver and pancreas due to some unknown toxin was probably primary and prior to pigment deposition.

Mallory<sup>1</sup> produced some interesting recent work on the etiology of hemochromatosis. His conclusions were that the disease is due to interference with the elimination of iron. He pointed out that normally from one twelfth to one twentieth of the total number of red blood cells are destroyed daily, and that failure to excrete the normal amount of iron would result in a marked accumulation of iron-containing products in the body. He considered the mechanism of this interference as probably due to chronic copper poisoning, in which the hemoglobin unites with copper to form cuprohemol. This substance is deposited in the tissues. The hemoglobin is then separated from the copper, and is changed to hemofuscin, an iron-containing compound with the iron bound in such a chemical fashion that it is incapable of reacting chemically to give the usual iron tests. By further action of the tissue enzymes the hemofuscin is changed to hemosiderin. These two substances act as foreign bodies and cause necrosis of the cells in which they lodge. Fibrosis follows, which produces dysfunction of the organs concerned. Mallory described hemofuscin and hemosiderin deposits in experimental animals as a result of poisoning them with small doses of copper over

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13 Gaskell, J. F., Sladden, A. F., Mackenzie Wallis, R. L., Vaile, P. I., and Garrod, A. E. A Contribution to the Study of Bronzed Diabetes, *Quart J Med* **2** 129, 1914.

14 McClure, C. W. Metabolism in a Case of Hemochromatosis, *Arch Int Med* **22** 610 (Nov.) 1918.

15 Howard, C. P., and Stevens, F. A. The Iron Metabolism of Hemochromatosis, *Arch Int Med* **20** 896 (Dec.) 1917.

16 Sheldon, J. H. The Iron Content of the Tissues in Hemochromatosis with Special Reference to the Brain, *Quart J Med* **21** 123, 1927. Dunn, J. S. Discussion of Hemochromatosis, *Brit M J* **2** 783, 1921. Telling, W. H. M. Discussion of Hemochromatosis, *Brit M J* **2** 784, 1921. Stewart, M. J. The Cirrhosis of Hemochromatosis, *Brit M J* **2** 1066, 1922.

17 Rous, P., and Oliver, J. Experimental Hemochromatosis, *J Exper Med* **28** 629, 1918.

long periods. He maintained that hemofuscin is deposited first and then changed to hemosiderin. This differs from the usual opinion. He showed the possible sources of human copper poisoning to be manifold: home brewed and distilled liquors, canned green vegetables colored with copper compounds and foods prepared in copper utensils in the presence of acids.

On inquiring into the histories of his patients, he found that some of them had worked with copper in machine shops for prolonged periods. He admitted that many patients present no such history, and that many copper workers do not contract the disease. However, the numerous, hitherto unrecognized sources of copper poisoning, and the marked differences in individual susceptibility to this substance, are considered by Mallory to be sufficient reason for these observations.

Hall and Butt<sup>18</sup> have obtained results similar to those of Mallory, but recently Flinn and von Glahn<sup>19</sup> created considerable doubt as to the validity of the foregoing hypothesis. They reported a pigmentation, similar to that described by Mallory, which they reproduced in rabbits' livers by the feeding of substances not containing copper, such as carlots and sodium acetate. Moreover, some of their rabbits developed pigment deposition on a normal laboratory diet. These experimenters failed to confirm Mallory's results in other animals.

Further work on this subject will be necessary to establish the similarity or difference between the types of pigmentation described by Mallory,<sup>1</sup> Hall and Butt,<sup>18</sup> Rous<sup>17</sup> and Flinn and von Glahn<sup>19</sup> before any conclusions on this subject can be formulated.

The history of our patient's metal work fits in with Mallory's hypothesis. We failed to demonstrate excess copper in tissue removed at biopsy, or in the blood or urine of our patient, but this failure merely duplicates that noted by Mallory. He explained this as being due to the fact that copper is present in the tissues of these patients in close combination with hemofuscin, where it cannot be demonstrated microchemically. As soon as the copper leaves this combination it is excreted. Sinclair,<sup>20</sup> in a case recently reported before the Association of American Physicians, discovered a greatly increased copper content in the liver, but his observation stands alone.

There remain a few isolated yet noteworthy points to be discussed.

In a paper entitled "Urinary Siderosis,"<sup>2</sup> Rous described a test in which the urinary sediments of patients with hemochromatosis, when

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18 Hall, E. M., and Butt, E. M. Experimental Pigment Cirrhosis Due to Copper Poisoning. Its Relation to Hemochromatosis, *Arch. Path.* **6**: 1 (July) 1928.

19 Flinn, F. B., and von Glahn, W. C. A Chemical and Pathological Study of the Effects of Copper on the Liver, *J. Exper. Med.* **49**, 5, 1929.

20 Sinclair, H. Paper to be published.

examined fresh or when stained by his modification of the Peil method, were found to contain pathognomonic amounts of hemosiderin. His results were not confirmed on three examinations of the urine from our patient. The cause may have been an inexpertness in technic. It seems probable, however, that there may be hemosiderin in the urine of one patient and not in that of another, depending on the amount of pigmentation in the kidney. Rendu and de Massary<sup>6</sup> and Mallory found pigment scarce in the kidney. The cause was ascribed to the fact that tubule cells desquamate as soon as they are destroyed by the hemosiderin accumulation within them. According to Mallory's view, urinary siderosis would be more readily discoverable in a case in which the copper poisoning was recent and hemosiderin deposition active, than in an "old" case such as ours.

The association of duodenal ulcer with hepatic disease is a circumstance which is being considered as possibly more than mere chance, since Mann's<sup>21</sup> work on the etiology of peptic ulcer, and its production by reducing in amount, or by side-tracking, the hepatic and pancreatic secretions which normally enter the duodenum. Our study of the literature, however, failed to reveal any other case of hemochromatosis associated with peptic ulcer.

In a recent case reported by Allan and Constam,<sup>22</sup> the patient similarly died of a terminal peritonitis, but no duodenal ulcer was found at autopsy.

Althousen and Kerr,<sup>23</sup> reporting on this disease since the development of insulin, noted the peculiar nature of the insulin reactions. One of their cases showed extraordinary instability of the blood sugar level and a tendency to sudden hypoglycemic shock. This is the type of insulin response we expected to find in our patient, but evidently the liver disease was not so great as to destroy the reserve function of the hepatic glycogenesis and glycogenolysis. He was resistant to insulin, and his case was similar in this and some other respects to the recent case of Allan and Constam.<sup>22</sup> The mechanism of this resistance is discussed in this paper.

Hypotension, sexual impotence, changes in the basal metabolism and loss of body hair have been alluded to in case reports of this disease.<sup>24</sup>

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21 Mann, F. C. Chemical and Mechanical Factors in Experimentally Produced Peptic Ulcer, *Tr. A. Am. Phys.* **42** 224, 1927.

22 Allan, F. N., and Constam, G. R. Insulin Resistance in a Case of Bronze Diabetes, *M. Clin. North America* **12** 1677 (March) 1929.

23 Althousen, T. L., and Kerr, W. T. Hemachromatosis, Report of Three Cases with a Result of Insulin Therapy in One Case, *Endocrinology* **11** 377, 1927.

24 Marsh, P. L. Hemosiderosis. A Case of "Bronze Diabetes" with Endocrine Disturbances (Sexual Regression), *Endocrinology* **8** 795, 1924.



They are doubtless the results of endocrine injury (i e, pigment cirrhosis), which is a frequent observation in hemochromatosis<sup>25</sup> Our patient showed several of these changes

The electrocardiogram accurately foretold the heart muscle damage found at autopsy

The preponderating left-sided hepatic enlargement noted in this patient has been mentioned as being present in other cases<sup>26</sup>

Three specimens of blood were sent to the laboratory for icterus index tests The report on each specimen stated that hemolysis had caused discoloration of the serum sufficiently to preclude the performance of the test Unfortunately, nothing was thought of this at that time, but it occurs to us that there might be some underlying factor, as yet not understood, which was responsible for this phenomenon on three separate occasions We merely report it as suggestive and deserving of further study

#### SUMMARY

A typical case of advanced hemochromatosis occurring in a metal worker is reported with detailed clinical, laboratory and autopsy observations The literature is briefly reviewed, and the possible etiologic rôle of chronic copper poisoning is discussed We feel that chronic copper poisoning has not yet been proved to be the cause of this disease

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25 Sprunt (footnote 12, first reference) Blanton and Healy (footnote 3)

26 Sprunt (footnote 12, first reference)

# EXPERIMENTAL LEFT AND RIGHT AXIS DEVIATION \*

CLAYTON J LUNDY, M D

AND

LEWIS W WOODRUFF, M D

CHICAGO

A method of placing and distending a balloon in various chambers of the heart and in the great vessels was previously described<sup>1</sup> This method permits electrocardiographic observation of the effect of increased pressure within and distention of the cardiac cavities and of obstruction to blood flow in the great vessels of the intact young dog under light ether anesthesia

This method of study has many undesirable features It is difficult to state what degree of pressure is exerted on adjacent structures With the balloon placed in the right ventricle, pressure might be exerted through the septum influencing the mitral or aortic orifices, or on the A-V node, His bundle, right bundle branch and its arborizations, or there could be interference with the flow of blood through the right ventricle by obstruction of the tricuspid orifice or of the entrance to the pulmonary artery orifice Likewise with the balloon in the left ventricle pressure might be exerted through the septum onto the tricuspid and pulmonary artery orifices, on the A-V node, His bundle, left bundle branch and arborizations or on the mitral and aortic orifices There are degrees of interference with the coronary circulation The normal movements of the contracting heart may be prevented, e g, the twisting of the heart on its own axis as it goes into systole With the balloon in the great vessels it is not certain that they are completely occluded especially on the arterial side When possible, efforts were made in various ways to reduce to a minimum the influence of these complicating factors Further work will be done observing arterial and venous blood pressure and rate of coronary flow A small balloon was used to cause the least amount of pressure on adjacent structures In the experiments on the left ventricle the right side of the heart was drained on both sides of the tricuspid valve in an attempt to obviate the influence of congestion within the pulmonary circulation and distention of the right side of the heart Since a single electro-

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\* From the Department of Medicine of Rush Medical College, University of Chicago

<sup>1</sup> Lundy, C J, and Woodruff, L W Experimental Heart Block, Arch Int Med **43** 184 (Feb) 1929

cardiograph was used, only one lead was properly standardized, the other was quickly thrown in and recorded without standardization. Since in this paper attention is paid chiefly to gross discordance of Q R S of leads I and III, it is felt that general conclusions are warranted.

There are some desirable features. The method is used on the intact dog. Complete recovery occurs. It is possible to influence separately either the right or the left ventricle. The experiments may be repeated many times on the same dog. It is desirable, however, to observe the position of the balloon at autopsy after each experiment.

### RESULTS

The balloon was placed entirely within the right ventricle and its pressure raised, while observing lead I, until a change in the electrocardiogram was noticed when a short observation of lead III was made. The change usually occurred at a pressure between that of systole and diastole as determined in the dog with a sphygmomanometer cuff around the abdomen compressing the abdominal aorta. In the dogs used, systolic pressure varied from 120 to 300 plus mm of mercury, and the diastolic pressure varied from 50 to 210 mm of mercury. On raising the pressure within the right ventricle Q R S<sub>1</sub> gradually became inverted, while Q R S<sub>3</sub> remained upright (fig 1). Immediately on release of the pressure Q R S<sub>1</sub> gradually returned to upright, while Q R S<sub>3</sub> remained upright. Repetition of the experiment on the same dog, lead III being used with frequent observations of lead I, showed Q R S<sub>3</sub> increase slightly in height while Q R S<sub>1</sub> had become inverted, on release of the pressure Q R S<sub>1-3</sub>, both rapidly returned to control form. These results produced a picture identical with that of right axis deviation.

Observations made with the balloon in the right auricle showed inversion of Q R S<sub>1</sub> late in the experiment after block had set in. With the balloon distending the tricuspid orifice (and seeming to vary with the simultaneous and proportionate distention of the right ventricle as compared with the right auricle), Q R S<sub>1-2-3</sub> became inverted. The time of appearance of the inversion of Q R S in all leads varied in different dogs between immediately appearing without slowing of the rate or without the appearance of block up to the time of the appearance of what seemed to be right bundle branch block. At times the inversion of Q R S in all leads set in after complete block had occurred, yet without marked slowing of the rate, and finally it also appeared after marked slowing of the rate, and the dog was practically pulseless.

After the picture of right axis deviation with the balloon in the right ventricle had been produced, it was expected that a picture of left axis deviation might as easily be produced with the balloon distend-

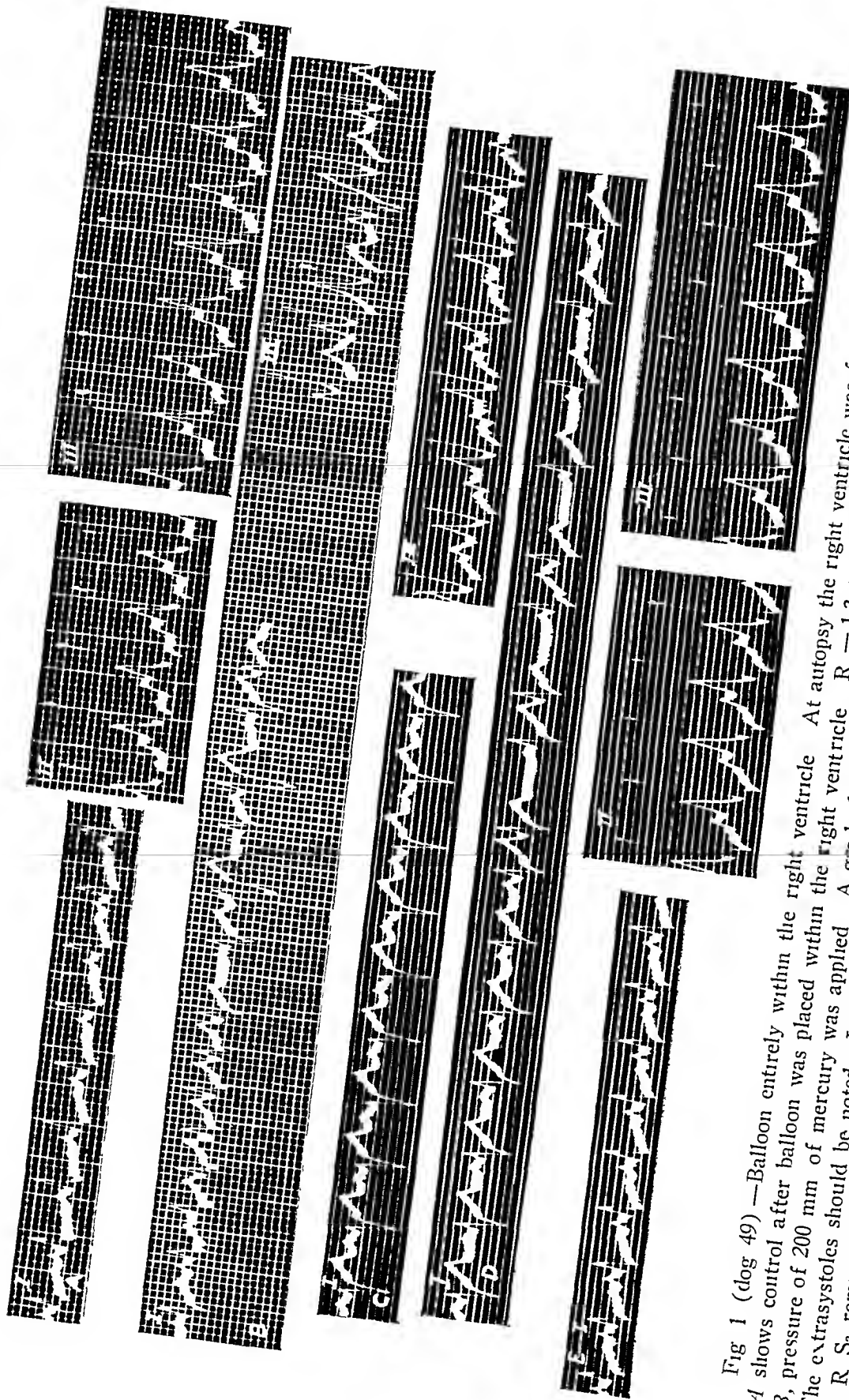


Fig 1 (dog 49) —Balloon entirely within the right ventricle At autopsy the right ventricle was found to be slightly dilated A shows control after balloon was placed within the right ventricle  $R = 13$  to 15 millivolts and  $R_s = 17$  to 15 millivolts The extrasystoles should be noted Lead III not standardized,  $1 \text{ cm} > 1 \text{ mv}$  C, complete inversion of Q R S1 occurred with gradual return of Q R S1 to upright Lead III not standardized,  $1 \text{ cm} > 1 \text{ mv}$  D, immediately after pressure was released, showing 1 mv except when otherwise specified The extrasystoles should be noted E, control after five minutes, showing recovery In all tracings the time intervals are of one-twenty-fifth second or 25 cm equals 1 second Standardization is 1 cm equals 1 mv except when otherwise specified White dots indicate limits of excursions

ing the left ventricle This was not true, however, for an entirely different situation was encountered A pressure higher than the systolic pressure of the dog was required The balloons available would not always withstand such high pressure When used, this high pressure often caused extrasystoles and even ventricular fibrillation, presumably because of embarrassment of the coronary circulation as well as of distention of the left ventricle Moreover, it was usually impossible to raise the left intraventricular pressure without causing congestion of the pulmonary circulation and right side of the heart with distention of the right ventricle This is due in part to the configuration of the left ventricular chamber on the septal side, which makes it rather easy to force the balloon against the aortic orifice and to obstruct the blood flow at that site The long cone-shaped character of the right ventricular chamber as it extends to the orifice of the pulmonary artery, together with the lower intraventricular pressure, permits a continuation of the circulation through that side of the heart in spite of the presence of the balloon

Attempts to overcome these difficulties were made by using a small balloon, and by inserting a cannula into the right ventricle, right auricle or superior vena cava and draining the right side of the heart about two seconds after the pressure was increased in the left ventricle Observations showed (fig 2) that on increasing the left intraventricular pressure,  $S_3$  would appear if absent before, or if present before would become increased from 0.2 and 0.3 millivolt to 0.4 and 0.5 millivolt, while  $R_3$  would diminish from 1.2 and 1.4 to 0.8 millivolt,  $R_1$  would increase in height The increased  $S_3$  lasts for but a few seconds when the wave almost and at times entirely disappears, while  $R_1$  and  $R_3$  both become increased in height When drainage from the right side of the heart was instituted, it was noted that  $S_3$  would again increase, at times more than when pressure was applied without drainage, and  $R_3$  would almost always show a corresponding diminution in height  $R_1$  was always increased in height under both circumstances When drainage of the right side of the heart was instituted before the initial increase of  $S_3$  disappeared, it would persist as long as the congestion of the right side of the heart was prevented Even when  $S_3$  had disappeared after its initial appearance or increase, drainage of the right side of the heart would cause it to reappear In experiments with and without drainage it was observed that  $S_3$  increased in height still further immediately after the increased left intraventricular pressure caused by the distended balloon was released, and this increase of  $S_3$  would persist until most of the water had been expelled from the balloon and then  $Q R S_{1-3}$  would both rapidly return to control form Drainage of the right side of the heart without pressure being applied within the left ventricle did not influence  $S_3$  in this manner, such

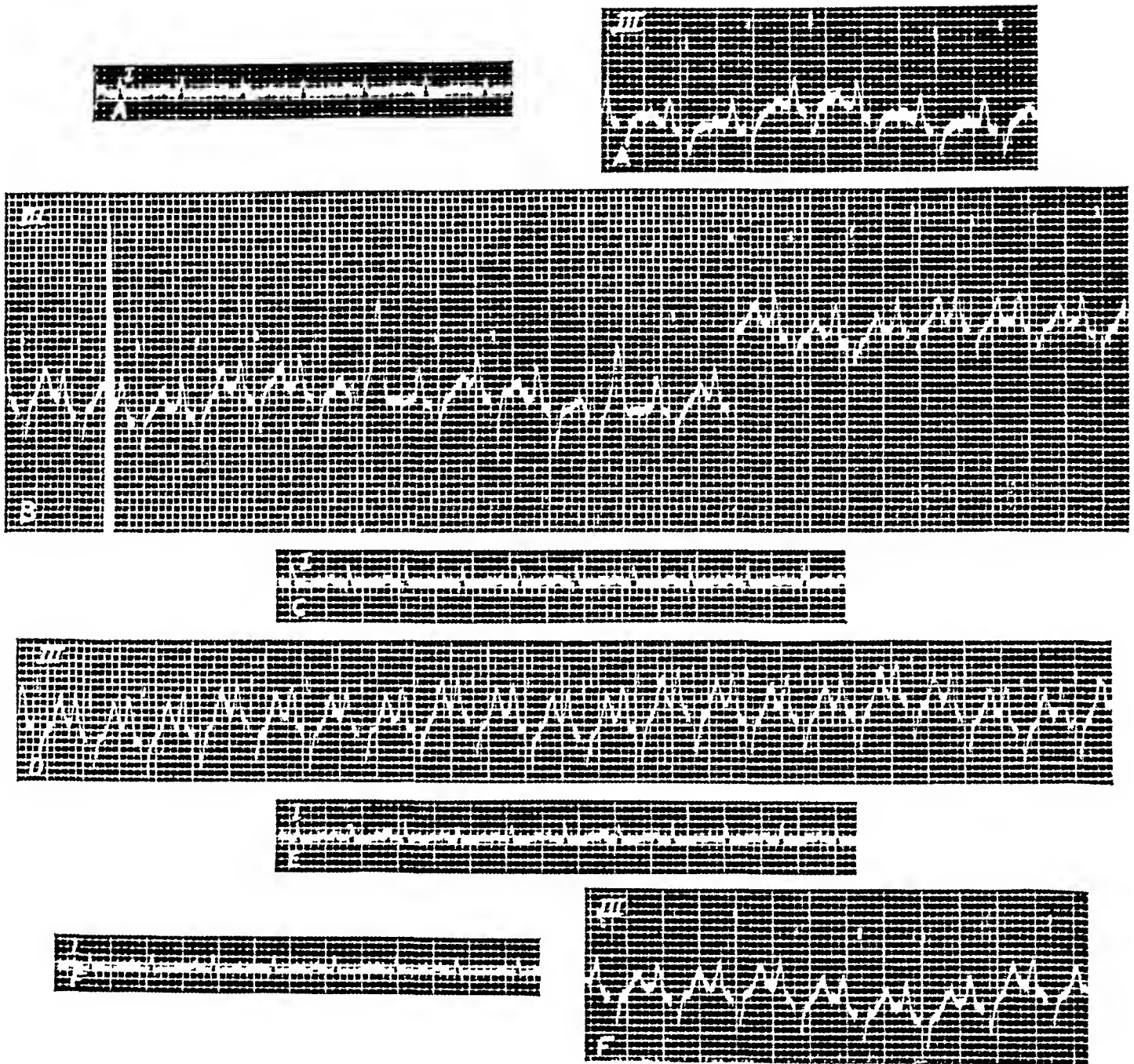


Fig 2 (dog 68) — Balloon entirely within the left ventricle *A* shows control with balloon in left ventricle and glass tube in right ventricle  $R_2 = 125$  to  $135$  millivolts,  $S_2 = 0.25$  to  $0.3$  millivolts *B*, pressure of  $340$  mm was applied at mark  $S_2$  increases from  $0.25$  and  $0.3$  to  $0.4$  millivolts within three seconds, diminishing to  $0.1$  and  $0.15$  millivolts immediately after  $R_2$  diminishes from  $1$  to  $0.8$  millivolts and within three seconds increases to  $1.6$  millivolts *C*, observation with pressure maintained shows  $R_1$  increased to  $0.2$  plus mv Lead I not standardized,  $1\text{ cm} < 1\text{ mv}$  *D*, during drainage of right side of heart with pressure maintained in the left ventricle  $R_2$  has diminished to  $0.6$  millivolt, while  $S_2$  has again increased to  $0.4$  millivolt *E*, observation during drainage of right side of heart  $R_1 = 0.15\text{ mv}$  Lead I not standardized,  $1\text{ cm} < 1\text{ mv}$  *F*, recovery after pressure released and drainage stopped  $R_1 = 0.15\text{ mv}$   $R_2 = 1.1$  to  $1.2$  and  $S_2 = 0.3\text{ mv}$

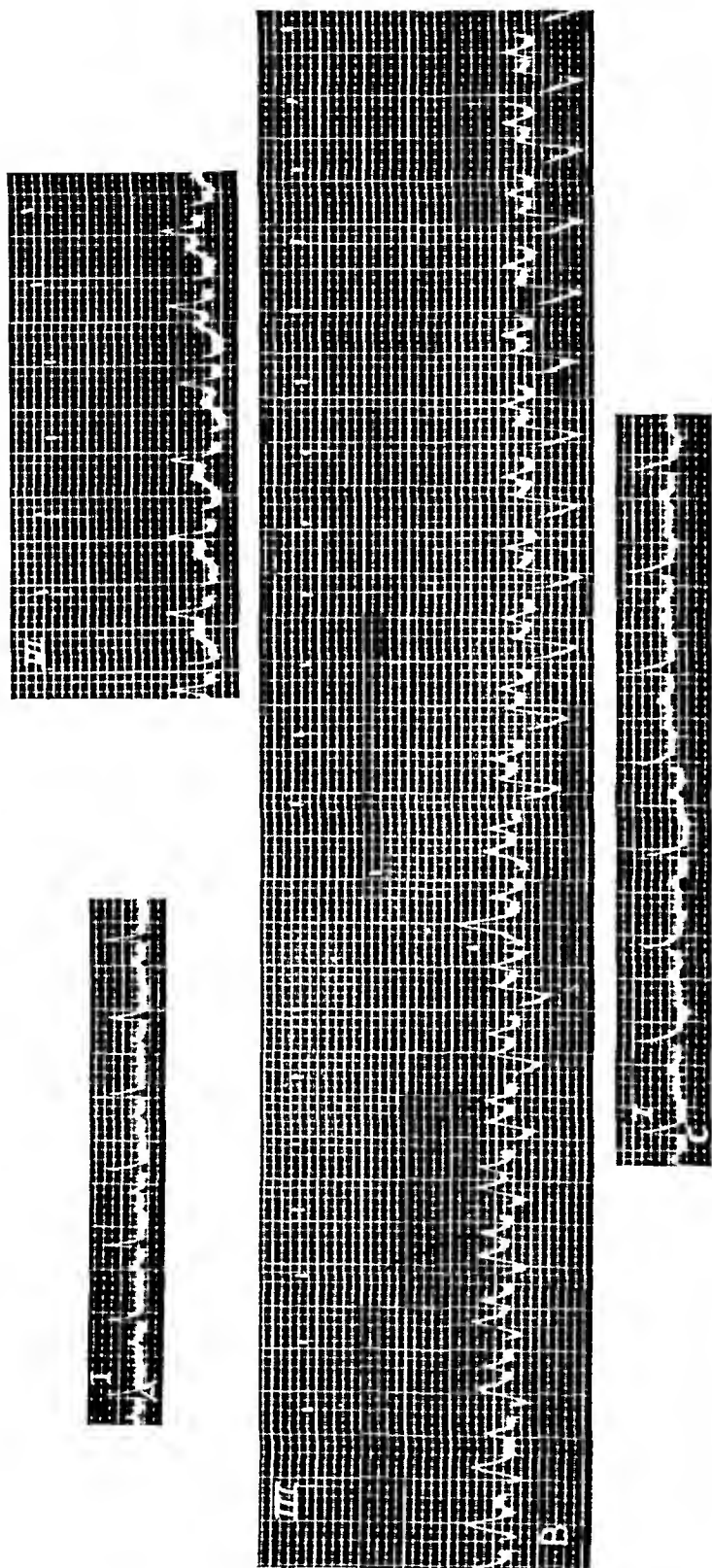


Fig 3 (dog 52) —Balloon at aortic orifice A shows control with balloon in aortic orifice  $R_1 = 0.38$  millivolt,  $R_2 = 1.9$  millivolt B, pressure suddenly raised to 440 mm of mercury  $R_2$  increased from 1.9 and 2 mv to 2.5 mv Note  $T_2$  inversion onset and extrasystole C, control observation while pressure was maintained  $R_1$  as high as 0.42 millivolt Lead I not standardized, 1 cm  $< 1$  millivolt



drainage could never be made at the same rate even when instituted under high negative pressure

These results show evidence of increased activity of the left ventricle and while not so marked as in the experiments on the right ventricle, they seem to be outside the limits of error and might be considered as a picture of a tendency to left axis deviation

Obstruction of the aorta at its orifice, or anywhere throughout its course, gave results similar to each other but no such evidence of increased activity of the left ventricle. In these experiments,  $Q R S_{1-3}$  both showed an increased height of R (fig 3)

A definite picture of left axis deviation was produced by placing the balloon in the inferior vena cava midway between the hepatic vein and right auricle (fig 4). On increasing the pressure sufficiently to obstruct the inferior vena cava,  $Q R S_3$  gradually became completely inverted while  $Q R S_1$  remained upright. Immediately on releasing the pressure,  $Q R S_{1-3}$  both returned to control form.

A fortunate accident enabled the production of a picture of left axis deviation in the intact dog by experimental pericardial effusion (fig 5). The balloon, on being inserted into the right side of the heart, became broken, and the tip of the glass tubing pierced the right auricle at the base anteriorly. On injection of water into the pericardial sac up to a pressure of 90 mm of mercury,  $Q R S_3$  rather rapidly became completely inverted, whereas  $Q R S_1$  remained upright but diminished in height. Release of the pressure caused prompt return to control form.

#### INTERPRETATION AND COMMENT

It seems advisable to attempt to explain why this apparently increased activity of one or the other ventricles of the heart is produced under the given conditions. Reflex action by way of the vagus has been ruled out. It should be needless to say that it was not due to hypertrophy because of insufficient time. It does not seem that it was produced by rotation of the heart on its own axis or by the heart as a whole being displaced to one side because the dogs were rotated to each side during the experiments, and this never caused the tracings to return to control form, nor was the glass tubing attached to the balloon seen to change its position except when the dogs themselves were rotated. With the balloon in the inferior vena cava it does not seem that there could be any disturbance of the position of the heart as a whole.

An interesting observation was made in two of the experiments on the right ventricle which might shed considerable light on the interpretation of the results in this entire group of experiments and in addition on the influence of cardiodynamic changes on heart action as well as on the interpretation of axis deviation. These observations



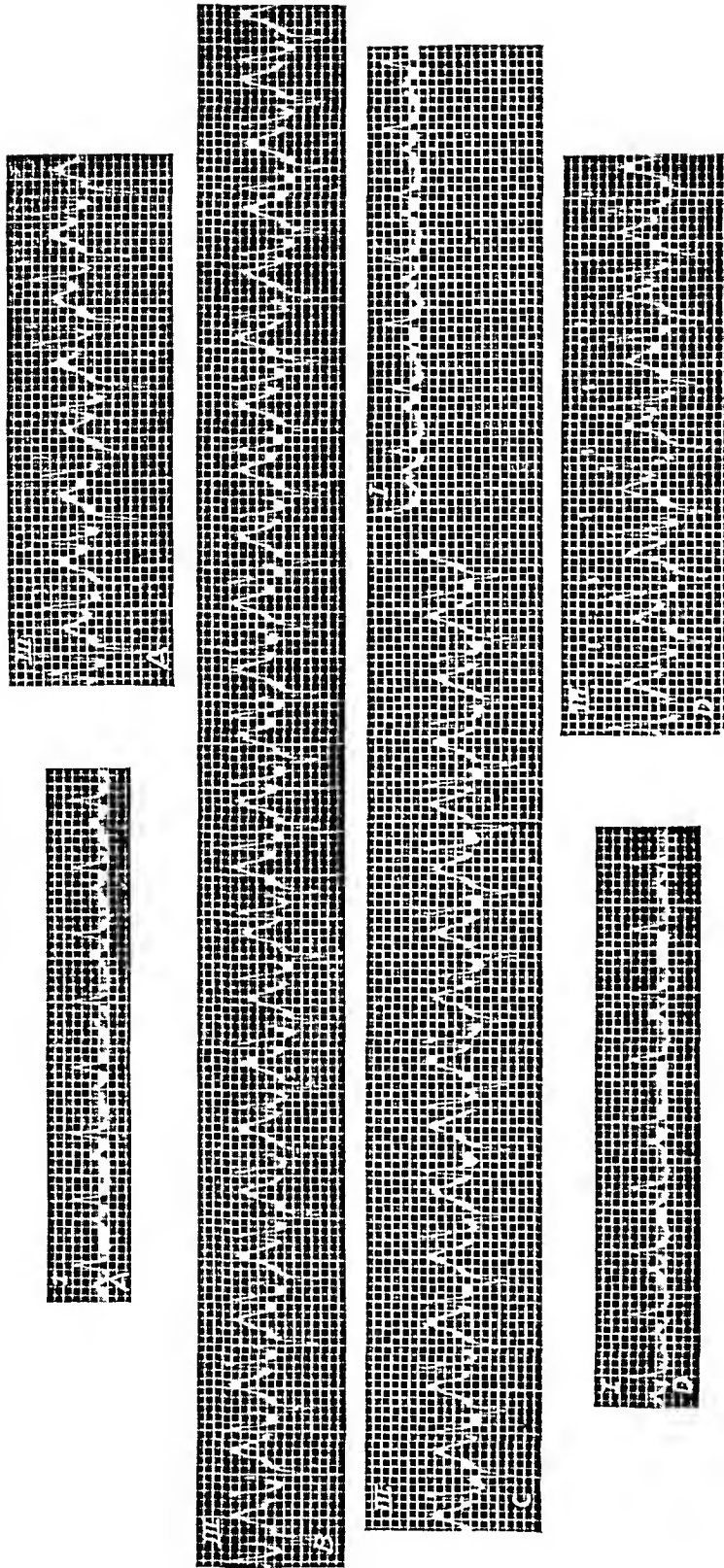


Fig 4 (dog 73) —Obstruction of inferior cava *A* shows control after balloon inserted into inferior vena cava  $R_1=0.3$  millivolt,  $R_3=0.6$  millivolt and  $S_3=0.5$  millivolt *B*, pressure 200 mm of mercury applied *Q*  $R$   $S_3$  shows gradual inversion  $R_1=0.1$  millivolt and  $S_3=0.45$  millivolt *C*, shows complete inversion of *Q*  $R$   $S_3$  with *Q*  $R$   $S_1$  remaining upright  $R_3=0.05$  millivolt,  $S_3=0.4$  millivolt and  $R_1=0.3$  millivolt Lead *I* not standardized, 1 cm  $< 1$  millivolt *D*, control after pressure is released  $R_1=0.32$  millivolt,  $R_3=0.9$  to 1 millivolt and  $S_3=0.3$  millivolt

are of special interest when considered in relation to the view of Eyster, Meek and Hodges<sup>2</sup> that dilation of the heart precedes hypertrophy. In these two experiments, right axis deviation was produced with the balloon in the right ventricle. Unlike the other experiments on the right ventricle, after release of the pressure, the tracings never returned to control form (fig 6). Q R S<sub>1</sub> remained diphasic, giving a more or less permanent right axis deviation. All of the experiments

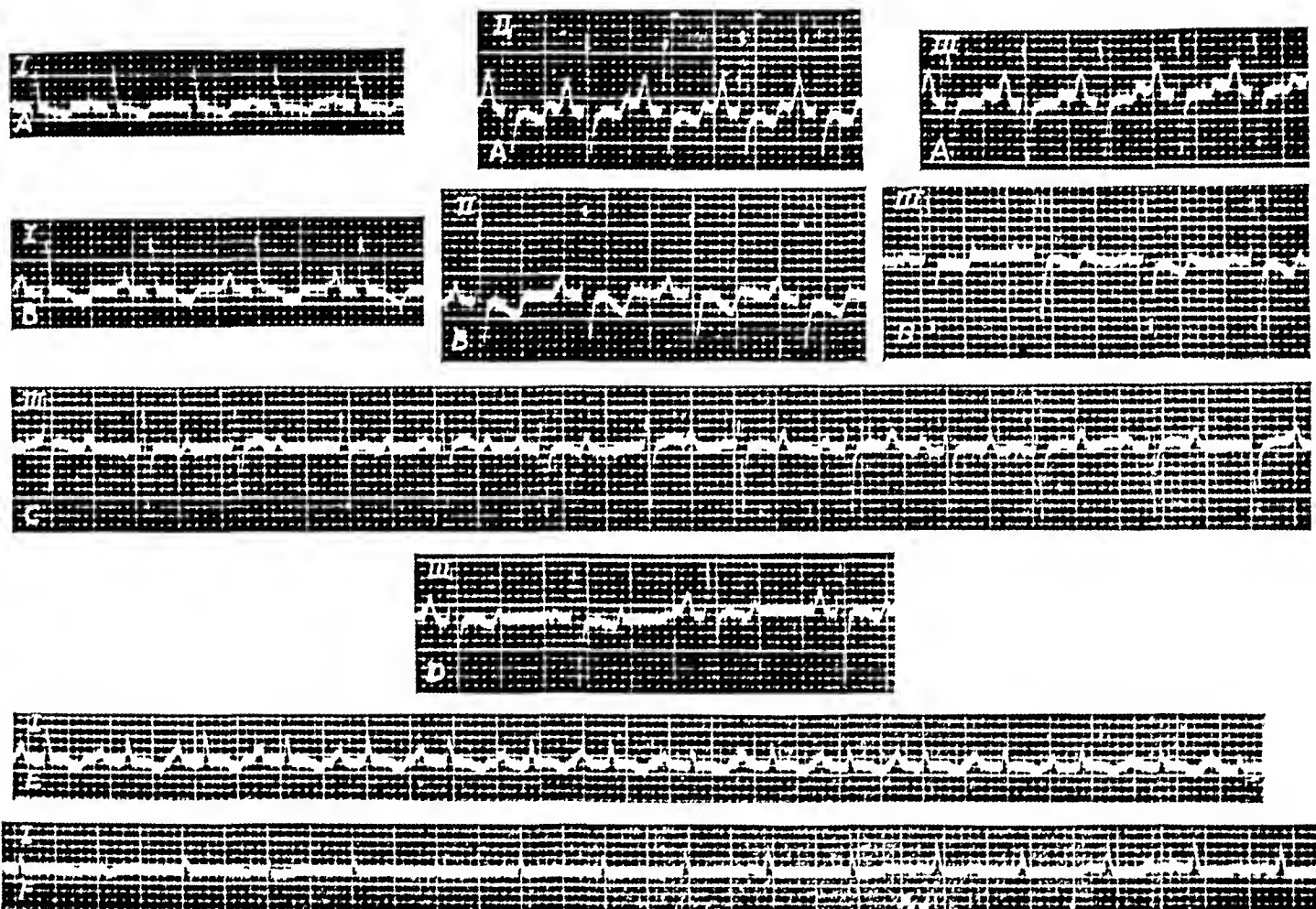


Fig 5 (dog 7)—Experimental pericardial effusion. *A* shows control before tube was inserted.  $R_1=0.4$  millivolt,  $R=0.6$  millivolt and  $S=0.5$  millivolt. *B*, control after tube was inserted and had perforated base of right auricle anteriorly. Note the notched  $P_{1-2-3}$ .  $R_1=0.55$  millivolt,  $R=0.6$  millivolt and  $S=0.6$  millivolt. *C*, pressure of 90 mm of mercury applied. Q R S<sub>1</sub> gradually becomes completely inverted. Note the diminished  $P_3$ .  $R_1$  goes to 0.1 millivolt and  $S_1$  goes to 0.7 millivolt. *D*, pressure released, Q R S<sub>1</sub> has returned to control form. *E*, pressure again increased to 60 mm of mercury. Q R S<sub>1</sub> gradually diminishes in height but remains upright. *F*, pressure released. Q R S<sub>1</sub> gradually returns to control height. Note failure of  $P_1$  to return to control height.

<sup>2</sup> Eyster, J. A. E., Meek, W. J., and Hodges, F. J. Cardiac Changes Subsequent to Experimental Aortic Lesions, *Arch Int Med* 39: 536 (April) 1927.

reported were crucial, and observations were never made after four or five hours and were usually made within a few minutes. Q R S<sub>1</sub> might have returned to control form if sufficient time had been given for recovery. But something had caused these two experiments to

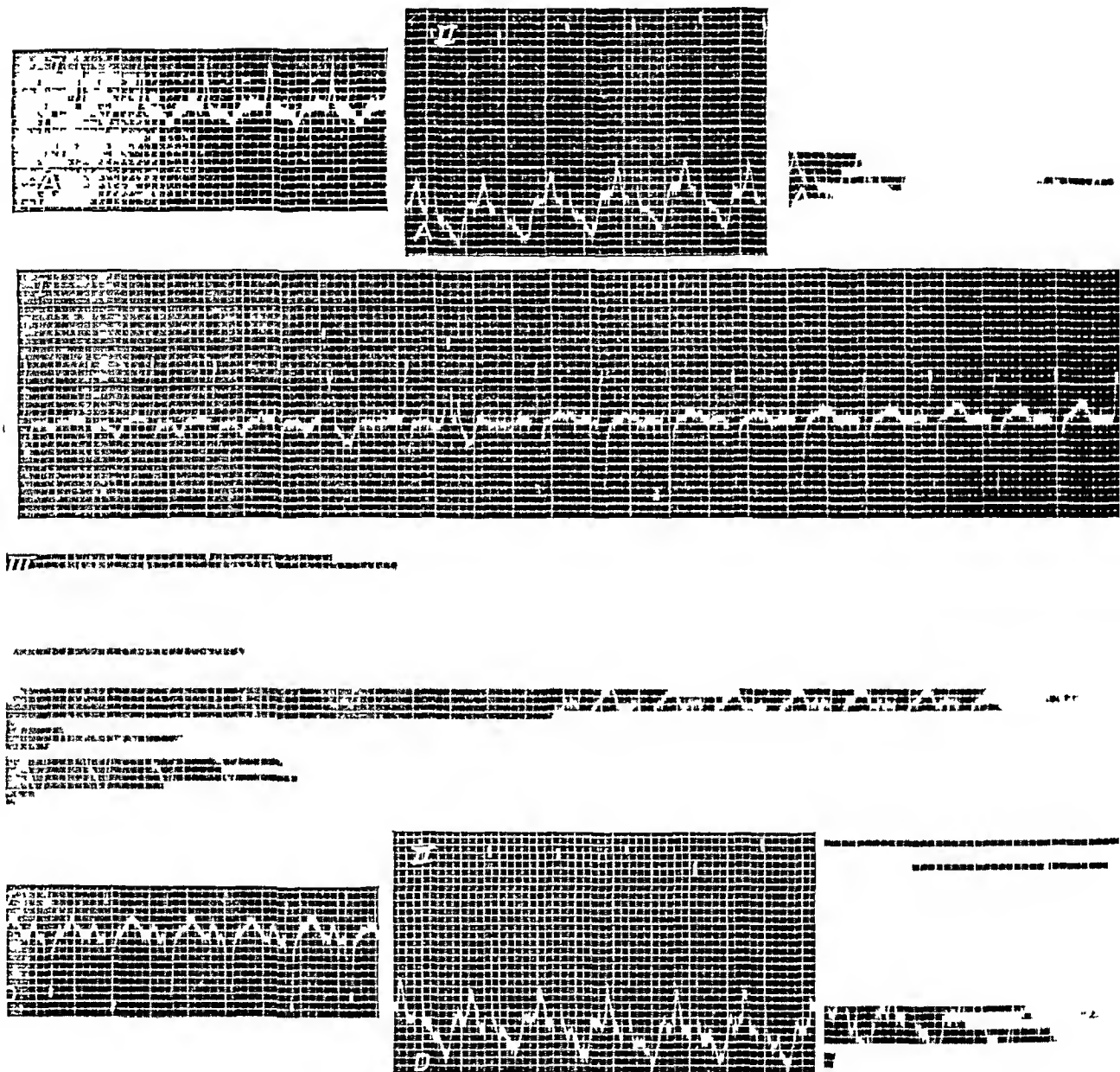


Fig 6 (dog 42) —Balloon entirely within right ventricle. At autopsy the right ventricle was found to be greatly dilated. A shows control after balloon was inserted into the right ventricle.  $R_1 = 0.55$  millivolt and  $R_3 = 1.6$  millivolt. B, pressure of 240 mm of mercury applied. Note the extrasystoles. Sudden appearance of deep S<sub>3</sub> with T<sub>3</sub> changing from inverted to upright. C, Q R S<sub>3</sub> remains upright. Q R S<sub>1</sub> as in B. Lead III not standardized, 1 cm > 1 millivolt. D, observation four hours later showing Q R S<sub>1</sub> remaining diphasic with Q R S<sub>2,3</sub> upright.

show a change which was more permanent than any similar experiment. At autopsy it was found that the right ventricle was greatly dilated, more so than in any of the other experiments on the right ventricle. It should be mentioned that the right ventricle was found to be somewhat dilated in all of the experiments, but this may have been due to the heart dying with the right ventricle in diastole. The left ventricle was found slightly dilated only in the experiments on the left ventricle, and only once was it found slightly more dilated than usual with no unusual electrocardiographic observations in that experiment.

The marked dilation of the right ventricle alone associated with a more permanent right axis deviation leads to the consideration of the influence of stretching the heart on its action current. We are not yet prepared to say that stretching the ventricle in this manner injured the individual cell membranes or whatever condition exists that delimits cells from each other. Eyster<sup>3</sup> reported a condition of "hydropic degeneration" found in dogs with dilatation of the whole heart. Dubrow<sup>4</sup> reported fatty degeneration more pronounced in the right ventricles of dogs showing right axis deviation subsequent to pneumothorax. The stretching of the muscle of the right ventricle produced a change associated with electrocardiographic evidence of increased activity of only that part of the heart which was stretched. Whatever the nature of the change may be, in most instances it was temporary, while in these two experiments it was more permanent.

Bayliss<sup>5</sup> said, "Increased permeability runs parallel with increased excitability of muscle." It might be said that the nervous impulse acting on heart muscle injured in this manner produces an increased action current because the stretched heart muscle is in a state of increased excitability. Further, if the permeability of the cell membrane is increased, or if the interfacial surface tension between cells is influenced, the state of increased excitability could be due to increased conductivity between cells because of the more ready diffusion of ions or electrolytes through the changed cell membranes, or interfacial surfaces of the cells, thereby lowering the resistance between cells. The lowered resistance between the cells of itself would give a stronger current as registered in the electrocardiographic record. This is consistent with an unvarying impulse conforming to Ohm's Law,  $\frac{\text{volts}}{\text{ohms}} = \text{amperes}$ . With such an interpretation of the mechanism involved, it could be said that the picture of right axis

3 Eyster, J. A. E. Cardiac Dilatation and Hypertrophy, *Tr. A. Am. Phys.* 42: 15, 1927.

4 Dubrow, J. L. Effect of Permanent Pulmonary Collapse on the Heart, *J. A. M. A.* 90: 1364 (April 28) 1928.

5 Bayliss, W. M. Principles of General Physiology, New York, Longmans, Green & Company, 1924, p. 398.

deviation was produced by stretching the right ventricle and thereby increasing its excitability. That this could be a matter of the degree of stretching of the heart muscle, permitting a more or less intimate contact between the electrolytes of the individual cells producing a proportionate degree of increased excitability, is a conjecture not without reason and evidence, for it was observed that when the right ventricle was moderately stretched, the right axis deviation rapidly returned to normal control form, whereas when the right ventricle was greatly stretched, it did not return to control form within four hours. In some experiments, for various reasons, we did not get so great a degree of axis deviation as in others. Similarly, the rate of propagation of the action current might be increased, as observed by shortened time of Q R S which usually returned to control length.

A fourth factor which could act in a similar manner might be due to the distended balloon partially obstructing the venous drainage of the heart and maybe only locally within the right ventricle. The partial asphyxia produced thereby might increase the permeability of the cell membrane, or it might influence the electrolytes of the cells making them more diffusible by changing their character or increasing their concentration. Factors operating in a different way could be fifth, change in the direction of the action current associated with change in the direction of the muscle fibers, sixth, a change in the relative volume or mass ratio between the right and left ventricles which might result (*a*) because the right ventricle is distended and (*b*) because the left ventricle might be actually smaller, owing to a diminished amount of blood being supplied to it.

The results obtained with the balloon at the tricuspid orifice are difficult to interpret. These observations have not been adequately controlled. No consideration is given to those instances of inversion after complete block had occurred with a greatly slowed rate and a practically pulseless dog. One similar clinical observation showed a similar downward deflection of Q R S in all leads, but  $P_1$  and  $T_1$  also were inverted, leading to the diagnosis of congenital dextrocardia with left axis deviation. The x-ray picture showed the heart and liver transposed. The inversion of Q R S in all leads of this group of experiments appears confusing, except that there seems to be a relationship to the balloon being in the aortic orifice in which Q R S of all leads increases in height and is directed upward. It is possible that right and left bundle branch block was produced when the balloon distended respectively the tricuspid and aortic orifices.

The picture of left axis deviation produced by obstructing the blood flow in the inferior vena cava may be due to increased peripheral resistance which could cause stretching of the left ventricle and maybe

increased excitability in a manner similar to that of the experiments on the right ventricle except that the blood damming back is the stretching agent. Here, too, the right ventricle would not be normally distended owing to diminished return flow of blood to the right side of the heart. This would decrease its relative volume or mass ratio even to a normally distended left ventricle. Also, the right ventricle might have a decreased action current owing to decreased excitability on the basis of the mechanism already described. These several factors operating together would further increase the tendency to left axis deviation.

The picture of left axis deviation produced by the experimental pericardial effusion was probably largely due to the extracardiac pressure interfering with the normal distention of the right ventricle more than the left, producing to a certain degree a relative left axis deviation. The incomplete filling of the right ventricle should be reflected back through the general circulation, causing greater distention of the left ventricle and some actual left axis deviation. In this regard it is interesting to observe that  $P_{1-2}$  were suppressed along with inversion of Q R S, and suppression of  $R_1$ , and that they did not always return to control form because the extracardiac pressure could not be reduced sufficiently to permit normal filling of the auricles. However, a sinus rhythm was maintained throughout.

With the balloon in the aortic orifice and in all divisions of the aorta,  $R_{1-3}$  were both increased in height. It is felt that this was probably because the right and left ventricles were distended almost simultaneously, owing to rapid congestion in the pulmonary circulation.

A satisfactory picture of left axis deviation was not produced with the balloon in the left ventricle, probably because of marked interference with the coronary circulation. However, it is felt that evidence of a tendency to left axis deviation was produced, and that it was due to the reasons already given. In these experiments on the left ventricle the factor of partial asphyxia may be more pronounced.

Clinical observation of shifting of the electrical axis in phasic variation unrelated to the respiratory rate is not uncommon. We have observed such shifting with Q R S, varying from entirely upright to completely inverted. In this connection we wish to report that in most of the seventy-three dogs observed in these experiments, a similar but less marked shifting of the electrical axis was seen in all leads, and more frequently after the heart had been weakened by the experimental procedure. It was observed often during marked tachycardia. It should be said that we have seen many clinical electrocardiograms with tachycardia which do not show this shifting. We have seen it most often in hearts with some degree of myocardial damage. It

seems that this shifting could be due to the flux of blood resulting from an imbalance of blood pressure and blood volume between the two ventricles causing gradual waxing and waning of the power of contraction of the separate ventricles, which might be due to corresponding variations of distention of the separate ventricles

The theory involved in these experiments is common knowledge of long standing Heidenhain and Hering<sup>6</sup> explained the production of extrasystoles as being due to dilation of the ventricles following ligation of the abdominal aorta Vaquez<sup>7</sup> definitely stated that he believes some extrasystoles are produced by "stretching" of the heart causing increased excitability The value of these experiments lies in the fact that each one of three chambers of the heart can be stretched separately This permits analysis of the results without the difficulty of interpreting the complicating influence of both sides of the heart being influenced almost simultaneously, as occurs on ligation of the aorta We observed many extrasystoles on introduction of the balloon into the heart and when the pressure was being raised Few were noticed while the pressure was maintained at a constant level, or when it was lowered

Clinical application of the mechanism presented herewith for increasing the excitability of the heart as a whole or in part is made to some extrasystoles It can readily be conceived that a heart damaged by local anemia would be weakened in that region Similarly, a heart, while equally injured throughout by toxic substances, might be conceived to have the effect of this injury produce more damage in certain areas than in others, owing to local causes such as a thinner heart wall, e g, at the apex and between the trabeculae carneae in the ventricles and between the muscle bands in the auricles Such weakened areas would probably be stretched more than the rest of the heart during the stress and strain of its activity, with the possible resultant increased excitability of such areas Such a view seems to be compatible with Mines' theory<sup>8</sup> of reentrant waves as a cause for some extrasystoles If such an application to extrasystoles should prove to be of value in determining their cause, of course the application would extend especially to related arrhythmias It should be unnecessary to state that caution, more experience and much deliberation will be required for a true evaluation of these experiments as giving evidence of the influence of cardiodynamics on the activity of the heart

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6 Heidenhain and Hering, quoted by Vaquez, H Diseases of the Heart, Philadelphia, W B Saunders Company, 1924, p 489

7 Vaquez, Henri Diseases of the Heart, Philadelphia, W B Saunders Company, 1924, p 489

8 Mines, G R Dynamic Equilibrium in the Heart, J Physiol 46 349, 1913

### SUMMARY

Factors operating in these experiments to produce electrocardiographic evidence of left or right axis deviation may be

- 1 Stretching of the muscle cells of the individual ventricles produced directly by the balloon or distention with blood may cause increased permeability of the cell membranes, thereby increasing the excitability of that individual ventricle with corresponding electrocardiographic evidence of axis deviation

- 2 The lowered resistance produced in this manner between the individual cells may account for a small part of the axis deviation

- 3 Partial asphyxia may cause an increased permeability of the cell membranes or may change the character or concentration of the electrolytes contained within the cells making them more diffusible

- 4 The rate of propagation of the action current may be increased

- 5 There may be a change in the direction of the action current associated with a change in the direction of the nerve fibers caused by distention with the balloon

- 6 There may be a change in the relative volume or mass ratio between the left and the right ventricles

- 7 Factors of decreased as well as increased excitability may be present

- 8 These factors in part or all may operate together

It is felt that some of these factors might give a more comprehensive idea of the influence of cardiodynamics on the activity of the heart

### CONCLUSIONS

- 1 Electrocardiographic evidence of right and left axis deviation was produced in the intact dog under ether anesthesia by distention of the respective ventricles

- 2 Acute dilation of the right ventricle was produced in the intact dog with corresponding right axis deviation

- 3 Possible factors for the production of axis deviation and various arrhythmias of the heart are suggested

- 4 The possible importance of these and similarly acting factors as a mechanism for clinical changes of the electrocardiogram is discussed



## Book Reviews

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BODILY CHANGES IN PAIN, HUNGER, FEAR AND RAGE By WALTER B CANNON  
Second edition Price, \$3 New York D Appleton & Company, 1929

In this second edition the author presents in the first eleven chapters an entirely logical sequence of the researches of many years on the autonomic system, the nervous control of the suprarenals and the sympathicomimetic function of "adrenin," including the external manifestations in the hair, pupils, etc, the increased blood sugar, the increased muscular blood flow, decreased peristalsis, increased cardiac action, restorative effects on muscular fatigue, increased coagulability of blood and increased number of red cells. In all of the conditions mentioned a close parallelism is shown between the changes occurring during pain, fear, rage and other violent emotions and the similar changes produced by "adrenin" therefore, proving, apparently, that "adrenin" is the producer of such changes normally during emotional excitement.

Beginning with the twelfth chapter the author distinguishes clearly between the facts as they are, and they do seem incontrovertible, and the interpretation of the data. To Cannon there is a definite utility of the body changes occurring in pain and great emotion. He is willing to admit, however, that this is a matter of opinion and offers to welcome a more reasonable theory when it appears. To psychologists the last few chapters on the energizing effects of emotional excitement and the denial of the evidence and interpretation on which the James-Lange theory of the emotions is based will furnish extremely stimulating reading. Hunger and thirst are discussed in an interesting fashion although here again there is room for difference of opinion. Cannon's theory of thirst reminds one somewhat of a much more elementary conception expressed by Francis Beaumont.

The intelligent layman and others who may believe in the eventual disappearance of war will find considerable pleasure in the last chapter, which deals with the substitution of international athletic competitions for the more destructive means of settling international disputes.

It is to be regretted that the book was published before the complete details on the sympathectomized animals produced by the author were available, as these animals show a definite ability to carry on the ordinary activities of a peaceful life but are completely inferior in respect to sudden readjustments required by the emergencies of life. The book is definitely a classic on the subject.

THE CLINICAL ASPECTS OF VENOUS PRESSURE By J A E EYSTER Price,  
\$2 50 New York The Macmillan Company, 1929

This book contains an excellent and clear discussion of the physiology of cardiac function and its relationship to arterial and venous pressure. The method of measuring venous pressure as devised by Hooker and Eyster and later modified by Eyster is given in full detail. The relationship of increased venous pressure to the various signs and symptoms of cardiac failure is adequately demonstrated, and it is pointed out that single readings mean little while the course of the venous pressure curve has much more significance. The author frankly admits that the usefulness of venous pressure estimation is limited to the narrow field of cardiac failure since a high venous pressure is found in practically no other general conditions. There is, however, no definite evidence that in the ordinary ambulatory case with fairly good cardiac reserve, a venous pressure determination would tell one more as to prognosis in regard to eventual failure than the ordinary careful history and examination of the patient. It is erroneous to draw conclusions from the cutaneous capillary pressures to those existing in the glomeruli, as does the author.

The bibliography is complete except for failure to mention the changes occurring in the venous pressure in pregnancy. On the whole this small volume will prove useful to physiologists and clinicians interested in the subject.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR VOLUME X NEUROPSYCHIATRY Price, \$2.25 Washington, D. C. United States Government Printing Office, 1929

Attention is called in the preface to the unusual opportunity offered to study statistically a large number of neuropsychiatric disorders with a uniform method of recording. It gives one a fairly accurate estimate of the percentage of nervous and mental disability present in the male population liable for military service, and also the types of nervous disorders which develop as a result of war activity. Attention is called to the large number of persons who in civil life passed as practically normal and who were actually suffering from a severe psychoneurosis which rendered them unfit for military duty. By far the most frequent cause for discharge was dementia praecox, mental deficiency second and epilepsy third. None of this group developed as a result of the war. The most important functional neurosis was "shell shock." The author states that there is still a controversy as to whether the cause of shell shock was mainly physical or mental. All, however, agree that the constitutional make-up of the person was a decided contributing factor.

A great deal of time and thought has been expended in the preparation of this volume and the results are most pleasing.

NEPHRITIS ITS PROBLEMS AND TREATMENT By T. I. BENNETT London Oxford Medical Publications

This volume contains a critical survey of nephritis and deals concisely with its clinical features and treatment. The author emphasizes the inadequacy of present forms of classification, but suggests that renal lesions of the type under discussion may occur as nephrosis, glomerulonephritis and arteriosclerosis with renal manifestations. He leans toward the conception that nephrosis is a part of a general metabolic disturbance in which the kidney shows only one phase. Infection is considered the most probable cause of glomerulonephritis. The author considers that arteriosclerosis with renal manifestations can best be explained by assuming that the arteriolar involvement antedates the renal changes, and that the nephritis is either a result of the vascular change, or due to the same cause which produces an abnormal condition of the arterioles.

Brief discussion of the more important symptoms is offered. The similarity between uremia and tetany is pointed out, particularly the low calcium content in the blood. Edema is considered as due to the causes of renal disease rather than to the nephritis.

Treatment for the various forms of renal disease is discussed, and lists of diets are appended.

TOBACCO AND PHYSICAL EFFICIENCY By PIERRE SCHRUMPF-PIERRE, M.D., Professor of Clinical Medicine, University of Cairo. Published under the Auspices of the Committee to Study the Tobacco Problem. Cloth Price, \$1.85 Pp. 134 New York Paul B. Hoeber, Inc., 1927

This monograph is the "first really complete compendium of the vast amount of literature of various countries concerning the effects of tobacco on the human system." As is the case with alcohol, the study of the effects of the use of tobacco is still incomplete. It has been difficult to obtain scientifically precise knowledge of the effect of tobacco on its users because of great variations in individual susceptibility, the forms of use as well as difference in grades and quality used and particularly the lack of data available as to the influence of tobacco as ordinarily used among large groups of people as compared with a similar group of abstainers. Well controlled clinical and laboratory studies are needed.

Therefore, no conclusions are drawn. Each chapter presents a fair, sane exposition of existing knowledge and opinion. An extensive bibliography of seventy-six pages is appended.

**PRINCIPLES OF MEDICAL TREATMENT** By GEORGE CHEEVER SHATTUCK, M D, A M, Harvard Medical School Sixth edition, revised and enlarged Cloth Price, \$3.50 Pp 256 Cambridge, Mass Harvard University Press, 1927

This edition has been greatly enlarged, both by the revision and expansion of material given in the earlier editions and by the addition of several new chapters on asthma, syphilis, lead poisoning, anemia, endocrine disorders, preoperative and postoperative medical treatment and vaccine therapy.

The principles of treatment are briefly elucidated and are based largely on accepted scientific knowledge. Many useful tables and diets are included and the chapter on medication deserves particular commendation, in that it is devoted to the intelligent use of relatively few drugs, vaccines, gland extracts, serums, etc.

The book should prove particularly valuable to the practitioner when time is available for quick reference only.

**ORIGIN OF MALIGNANT TUMORS** By THEODOR BOVERI Translated by Marcella Boveri Price, \$2.50 Baltimore Williams & Wilkins Company, 1929

Another theory for the development of malignant tumors is added to the long list. The author's work on mitoses in eggs of sea urchins serves as the basis for his belief that tumors arise from a single primordial cell, and that their characteristics as neoplastic cells are due to a "wrongly combined chromosome complex." This abnormality in distribution of chromosomes is the result of multipolar mitosis brought about by a variety of conditions. Little is said concerning what these conditions are. Admitting the author's theory we are thus still without knowing the cause of malignant tumors, the theory propounded being, in the last analysis, concerned only with the mechanism of neoplastic development once this has begun.

The volume is primarily of interest to the cytophysiologist. The style makes it difficult reading for others. This treatise, however, should serve to stimulate further interest in the study of the individual neoplastic cells. Many questions for investigation along these lines are suggested.

**THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR VOLUME XII PATHOLOGY OF THE ACUTE RESPIRATORY DISEASES AND OF GAS GANGRENE** Price, \$3.60 Washington, D C United States Government Printing Office, 1929

The first 405 pages are given over to the discussion of respiratory infections, the remaining 170 pages to gas gangrene.

The pathology is discussed in detail, and this volume will serve as an accurate source of information for future generations. The volume is profusely illustrated with both black and white and colored plates of gross and microscopic specimens.

## CORRECTION

The date of submission of the article by Dr Benjamin I Ashe, entitled, "The Hemoglobin Percentage and the Red Blood Cell Count in Bright's Disease, Myocardial Insufficiency and Hypertension," was incorrectly given in the October issue (44 506 1929). It should read February, 1929, instead of June 18, 1929.

# INDEX TO VOLUME 44

Book Reviews are grouped together and are indexed under that heading in alphabetical order, under the letter B

	PAGE		PAGE
Adams, L I Tuberculosis of aorta, report of case	711	Blood—Continued	
Adenoma, toxic of thyroid	73	eosinophilic hyperleukocytosis in Hodg- kin's disease with familial eosinophilic diathesis	772
Adrenals See Suprarenals		hemoglobin percentage and red blood cell count in Bright's disease myocardial insufficiency and hypertension	506
Allan, F N Hyperinsulinism, report of 2 cases	65	inorganic serum sulphates in renal insuf- ficiency, study of blood urea and cre- atinine, effect of diuresis on serum sulphates	211
Amino Acids content of blood in health and disease	351	pressure and weight	877
Ammonium chloride, chemical study of urine effected by combinations of methenamine and	252	pressure arterioles in cases of hyper- tension	395
Anderson, E W The arterioles in cases of hypertension	395	pressure effect of purine base diuretics on coronary flow	118
Anemia, reticulocytosis produced by liver extract, 2 3 and 4 hour interval observations	502	pressure effect of sodium chloride on hypertension	531
Aorta, tuberculosis of	711	pressure, hemoglobin percentage and red blood cell count in Bright's disease, myocardial insufficiency and hyper- tension	506
Areher, B H Sugar tolerance in arthritis, arthritis of menopause	238	pressure in diabetes mellitus, statistical study	797
Sugar tolerance in arthritis, chronic in- fections arthritis	37	pressure, systolic in duodenal and gastric ulcer	843
Arteries, arterioles in cases of hyperten- sion	395	pressure, variability of	229
coronary, effect of purine base diuretics on coronary flow	118	reticulocyte count in normal and abnor- mal conditions	208
Arthritis, sugar tolerance in	37, 238	sugar, hepatogenic hypoglycemia asso- ciated with primary liver cell carci- noma	700
Artichokes, failure of diabetic patient to utilize dried powder	362	sugar of normal and of diabetic subjects, effect of uncooked starch on	341
Ashe, B Hemoglobin percentage and red blood cell count in Bright's disease, myocardial insufficiency and hyper- tension	506	sugar, regulation in idiopathic steator- rhea (sprue and Gee-Herter's disease)	17, 477
Atelectasis See under Lungs		Blueberry Leaf Extract, overdosage	204
Bacillus coli treatment of pyuria due to	303		
Baker, B M Jr Undulant fever present- ing clinical syndrome of Intermittent hyarthrosis	128	BOOK REVIEWS	
Bannick, E G Renal insufficiency asso- ciated with Bence-Jones proteinuria, report of 13 cases with note on changes in serum proteins	486	Bedeutung des Retikuloendothelialsys- tems für das Streptokokkenseptispro- blem, N Louros and H L Scheyer	784
Barry, F S Prolongation of life of nephrectomized dogs with production of edema	424	Bodily Changes in Pain, Hunger, Fear and Rage, W B Cannon	908
Brumgartner, C J Malignant lesions of gallbladder	735	Cardiac Arrhythmias, I R Roth	302
Berger, S S Effect of sodium chloride on hypertension	531	Climacteric (The Critical Age) G Mar- anon	153
Bernstein, M Boeck's sarcoid, report of case with visceral involvement	721	Clinical Aspects of Venous Pressure, I A E Eyster	908
Bile secretion in response to rectal instil- lations	455	Clinical Electrocardiograms Their Inter- pretation and Significance, F A Willius	623
Blood amino acid content of, in health and disease	351	Das Exsiccoseproblem, E Schiff	302
coagulation, effect of mechanical con- striction of hepatic veins, with refer- ence to	676	Diabetes Latente, F Puchulu	301
		Fluorptologia clinica e sperimentale della lipemia, M Bufano	785
		Gallensekretion und Gallenentleerung, D Adlersberg	786
		Index to Symptomatology Edited by H L Tidy	464
		International Medical Annual A Year Book of Treatment and Practitioner's Index	623
		Krankheiten des Herzens und der Ge- fisse, E Edens	621
		Luremie convulsive, H Thiers	786
		Medical Department of the United States Army in the World War Volume X Neuropsychiatry	909

# INDEX TO VOLUME 44

BOOK REVIEWS—Continued	PAGE		PAGE
Medical Department of the United States Army in the World War Volume XII Pathology of the Acute Respiratory Diseases and of Gas Gangrene	910	Constipation, motility of rectum in normal and in constipated subjects	147
Modern Medicine Its Theory and Practice in Original Contributions by American and Foreign Authors Edited by Sir W Osler	464	Cook, J E Rate of glycolysis in erythremia (polycythemia vera)	813
Morphologic Variation and the Rate of Growth of Bacteria, A T Henrici	621	Copper poisoning as probable etiologic cause of hemochromatosis	882
Muscle Function, W G Wright	463	Cornell, V H Bromsulphalein hepatic function test, report of a series of tests	818
Nephritis Its Problems and Treatment, T I Bennett	909	Dailey, M E Cerebrospinal fluid in myxedema	368
Old Age, A S Warthin	784	Dextrose, sugar tolerance in arthritis	37, 238
Origin of Malignant Tumors, T Boveri	910	Diabetes bronze	882
Practical Clinical Laboratory Diagnosis, C C Bass and F M Jones	786	diabetes mellitus, blood pressure in, statistical study	797
Praktische differentialdiagnostik für Aerzte und Studierende VI Haut- und Geschlechtskrankheiten I Hautkrankheiten, P Tachau	301	diabetes mellitus, failure of diabetic patient to utilize dried artichoke powder,	362
Principles of Clinical Pathology in Practice, G Bourne and K Stone	301	diabetes mellitus, effect of uncooked starches on blood sugar of normal and of diabetic subjects	344
Principles of Medical Treatment, G C Shattuck	910	diabetes mellitus, overdosage of blueberry leaf extract	204
Probleme de la sensibilité viscerale et l'anesthésie des splanchnalgies, A Lemaire	622	diabetes mellitus, pathologic changes in spinal cord and peripheral nerves in	576
Progressive Relaxation A Physiological and Clinical Investigation of Muscular States and Their Significance in Psychology and Medical Practice, E Jacobson	622	diabetes mellitus, pathology of pancreas in non-diabetic persons, study of 156 consecutive autopsies on nondiabetic patients	663
Tobacco and Physical Efficiency, P Schrumpf-Pierron	909	Diaphragm influence of, on esophagus and stomach	856
Treatment of Varicose Veins by Intravenous Injections, J P L McLatchie	463	Dialysis, effect of treatments on temperature	556
Tumores primitivos de la pleura, J W Tobias	463	Dickson, W H Rate of evacuation of various foods from normal stomach preliminary communication	787
Untersuchungen ueber Porphyrin mit Besonderer Berücksichtigung de Porphyrin congenita, M Borst and H Konigsdorffer Jr	623	Diehl H S Variability of blood pressure study of systolic pressure at 5 minute intervals	229
William Harvey, A Mallock	785	Digestive tract, physiology, rate of evacuation of various foods from normal stomach	787
Brandes W W Effect of mechanical constriction of hepatic vein, with special reference to coagulation of blood	676	Disease constitutional variation and susceptibility to	625
Bright's Disease See Nephritis		Diuresis and Diuretics, action of merbaphen on kidney of dog	438
Bromsulphalein hepatic function test	818	diuretic action of parathyroid extract	374
Brown G E Systolic blood pressure in duodenal and gastric ulcer, statistical study	843	edema in congestive heart failure, effectiveness of diuretics as guide to prognosis	465
Brown, W H Constitutional variation and susceptibility to disease	625	purine base diuretics effect of on coronary flow	119
Caffeine effect of purine base diuretics on coronary flow	118	Duodenal Tube, improved its advantages with brief outline of duodenal intubation	71
Calcium content of cerebrospinal fluid effect of parathyroid extract on diffusibility of calcium in human beings	834	Duodenal Ulcer See Peptic Ulcer	
Cancer of renal cortex with factors bearing on prognosis	746	Edema in congestive heart failure effectiveness of diuretics as guide to prognosis	465
primary liver cell, hepatogenic hypoglycemia associated with	700	prolongation of life of nephrectomized dogs, with production of	424
Cantarow A Calcium studies, calcium content of cerebrospinal fluid	667	Eosinophilia hyperleukocytosis in Hodgkin's disease with familial eosinophilic diathesis	772
Calcium studies, effect of parathyroid extract on diffusibility of calcium in human beings	834	Epilepsy, pathologic aspect of	142
Celiac Disease regulation of blood sugar in idiopathic steatorrhea (sprue and Gee Herter's disease)	17	Erythremia, rate of glycolysis in	813
Cerebrospinal Fluid, calcium content of in myxedema	368	Esophagus influence of diaphragm on stomach and	856
relation of withdrawal of to body temperature, consideration of a thermoregulatory center, study of 250 cases	263	Fenn G K Effect of purine base diuretics on coronary flow	118
Chest See Thorax		Fineberg M H Effect of sodium chloride on hypertension	531
Cinchophen toxic cirrhosis of liver due to	281		

# INDEX TO VOLUME 44

	PAGE		PAGE
Fitz-Hugh, T Jr Hemochromatosis in a metal worker, case report with autopsy and brief review of literature	882	Hydrarthrosis, intermittent undulant fever presenting clinical syndrome of	128
Foods, rate of evacuation of various foods from normal stomachs	787	Hyperinsulism	65
Friedlander, A Reticulocyte count in normal and abnormal conditions	209	Hypertension See Blood Pressure	
Fructosuria	47	Hypoglycemia See Blood Sugar	
Fry, E G Opium addiction, excretion of morphine by human addicts,	862	Industrial diseases, hemochromatosis in a metal worker	882
Gallbladder, malignant lesions of	735	Intestines, obstruction, and septic invasion of peritoneum, combined medical and surgical treatment	543
Garbat, A L Secretion of bile in response to rectal instillations	455	Irving, H Reticuloecytosis produced by liver extract, 2, 3 and 4 hour interval observations	502
Gastric Ulcer See Peptic Ulcer		Ivy, A C Motility of rectum in normal and in constipated subjects	147
Gee-Herter's Disease See Celiac Disease		Prolongation of life of nephrectomized dogs with production of edema	424
Ghrist, D G Blood pressure and weight	877	Iacobi, H G Secretion of bile in response to rectal instillations	455
Gilbert, N C Effect of purine base diuretics on coronary flow	118	Joannides, M Influence of diaphragm on esophagus and stomach	856
Ginsburg, S Toxic adenoma of thyroid	73	Johansen, A H Treatment of pyuria due to bacillus coli	303
Glycolysis rate of, in erythremia (polycythemia vera)	813	Johnstone, B I Action of merbaphen (novasurol) on kidney of dog, combined functional and pathologic study	438
Goldring W Edema in congestive heart failure, effectiveness of diuretics as guide to prognosis	465	Judd, E S Carcinoma of renal cortex with factors bearing on prognosis	746
Gordon, A Relation of withdrawal of cerebrospinal fluid to body temperature, consideration of a thermoregulatory center, study of 250 cases	263	Malignant lesions of gallbladder	735
Pathologic aspect of some epilepsies	142	Keith, H M Action of merbaphen (novasurol) on kidney of dog combined functional and pathologic study	438
Greene, C H Disease of liver, various types of syphilis of liver and tests for hepatic function	155	Keith N M The arterioles in cases of hypertension	395
Renal insufficiency associated with Benedict-Jones proteinuria, report of 13 cases with note on changes in serum proteins	486	Kernohan, J W The arterioles in cases of hypertension	395
Hand J R Carcinoma of renal cortex with factors bearing on prognosis	746	Kidneys, carcinoma of renal cortex with factors bearing on prognosis	746
Hartman, H R Benign gastric and duodenal ulcers, clinical diagnosis and conditions found at operation	314	disease inorganic serum sulphates in renal insufficiency	244
Blood pressure and weight	877	renal insufficiency associated with Benedict-Jones proteinuria	486
Systolic blood pressure in duodenal and gastric ulcer, a statistical study	843	Secretion See Diuresis and Diuretics	
Heart, edema in congestive failure, effectiveness of diuretics as guide to prognosis	465	thrombo-angioneurotic changes of, in chronic nephritis	272
experimental left and right axis deviation	893	Konzelmann, I W Boeck's sarcoid report of case with visceral involvement	721
hemoglobin percentage and red blood cell count in Bright's disease, myocardial insufficiency and hypertension	506	Lees, H D Variability of blood pressure, study of systole pressure at 5 minute intervals	229
pneumotachograph in certain intrathoracic diseases, its diagnostic value	289	Opium addiction, effects of abrupt withdrawal followed by readministration of morphine in human addicts, with reference to composition of blood, circulation and metabolism	1
Heeres, P A Fructosuria	47	Opium addiction, effects of intramuscular and intravenous administration of large doses of morphine to addicts	376
Hemochromatosis in a metal worker, case report with autopsy and review of literature	882	Opium addiction, excretion of morphine by human addicts	862
Hennell, H Massive pulmonary atelectasis (collapse), mechanism and clinical significance	604	Opium addiction, general summary	370
Heyl, F W Chemical study of urine as effected by combinations of ammonium chloride and methenamine	252	Opium addiction, study of effects of seopolamine treatment for morphine addiction	194
Hines, L E Motility of rectum in normal and in constipated subjects	147	Opium addiction water balance studies during administration and withdrawal of morphine	693
Hoehlein, M Pneumotachograph in certain intrathoracic diseases, its diagnostic value	289		
Hodgkins Disease See Lymphogranuloma			
Hueper, W C Diuretic action of parathyroid extract	374		

# INDEX TO VOLUME 44

	PAGE		PAGE
Liver, bromsulphalein hepatic function test	818	Nurnberger, P Effects of diathermy treatments on temperature	556
effect of mechanical constriction of hepatic vein, with special reference to coagulation of blood	676	O'Leary, P A Diseases of liver, various types of syphilis of liver and tests for hepatic function	155
extract reticulocytosis produced by, 2, 3 and 4 hour interval observations	502	Opium Addiction, effects of abrupt withdrawal followed by readministration of morphine with reference to composition of blood, the circulation and metabolism	1
hepatogenic hypoglycemia associated with primary liver cell carcinoma	700	effects of intramuscular and intravenous administration of large doses of morphine	376
toxic cirrhosis due to cinchophen	281	effects of scopolamine treatment for morphine addiction	194
various types of syphilis with reference to test for hepatic function	155	excretion of morphine by human addicts	862
Lueth, H C Motility of rectum in normal and in constipated subjects	147	general summary	870
Lundy, C J Experimental left and right axis deviation	893	water balance studies during administration and withdrawal of morphine	693
Lungs, atelectasis, massive pulmonary (collapse) its probable mechanism and clinical significance	604	Pancreas, pathology of, in non-diabetic persons, study of 156 consecutive autopsies on nondiabetic patients	663
pneumotachograph in certain intrathoracic diseases, its diagnostic value	289	report of 2 cases of hyperinsulinism	65
Lymphogranuloma eosinophilic hyperleukocytosis in Hodgkin's disease, with familial eosinophilic diathesis	772	Parathyroid Extract diuretic action of effect of, on diffusibility of calcium in human beings	374
Lyon, L E Prolongation of life of nephrectomized dogs with production of edema	424	Peptic Ulcer, benign gastric and duodenal ulcers, clinical diagnosis and conditions found at operation	303
Major S G Blood pressure in diabetes mellitus, a statistical study	797	systolic blood pressure in duodenal and gastric ulcer	843
Meningo-encephalitis due to torula histolytica	560	Peritoneum intestinal obstruction and septic invasion of, combined medical and surgical treatment	543
Menopause arthritis of	238	Petrici, L Systolic blood pressure in duodenal and gastric ulcer	843
Merbaphen action of, on kidney of dog	438	Phillips, K Intestinal obstruction and septic invasion of peritoneum, combined medical and surgical treatment	543
Methenamine, chemical study of urine as effected by combinations of ammonium chloride and	252	Pituitary Body and suprarenal cortex	339
Moehlig R C Pituitary gland and suprarenal cortex	339	Pneumotachograph in certain intrathoracic diseases, its diagnostic value	289
Morphine addiction, effects of scopolamine treatment for	194	Polycythemia vera See Erythremia	
effects of abrupt withdrawal followed by readministration in human addicts with reference to composition of blood the circulation and metabolism	1	Porter, W B Reticulocytosis produced by liver extract, 2, 3 and 4 hour interval observations	502
effects of intramuscular and intravenous administration of large doses of to human addicts	376	Proteinuria See under Urine	
excretion by human addicts	862	Purina See Urine, pus	
water balance studies during administration and withdrawal of	693	Rectum, motility of in normal and in constipated subjects	147
Myrtomel See Blueberry leaf extract		Reichle, H S Toxic cirrhosis of liver due to cinchophen	281
Myxedema cerebrospinal fluid in	368	Reticulocytosis See Anemia	
Nadler, W H Hepatogenic hypoglycemia associated with primary liver cell carcinoma	700	Richards, C V An improved duodenal tube, brief outline of duodenal intubation	71
Nephrectomy, prolongation of life of nephrectomized dogs with production of edema	424	Rivers, A B Benign gastric and duodenal ulcers, clinical diagnosis and conditions found at operation	314
Nephritis chronic, thrombo-angioneurotic changes of kidneys in	272	Rosenthal, S M Effect of uncooked starches on blood sugar of normal and of diabetic subjects	344
hemoglobin percentage and red blood cell count in Bright's disease, myocardial insufficiency and hypertension	506	Rowntree L G Diseases of liver, various types of syphilis of liver and tests for hepatic function	155
Nerves peripheral pathologic changes in spinal cord and, in diabetes mellitus	576		
Norgaard, A Regulation of blood sugar in idiopathic steatorrhea (sprue and Gee-Herter's disease), low blood sugar curve	17		
Novasurol See Merbaphen			

# INDEX TO VOLUME 44

	PAGE		PAGE
Sarcoid, Boeck's, case with visceral involvement	721	Temperature of body, relation of withdrawal of cerebrospinal fluid to, consideration of a thermoregulatory center	263
Schmidt, E G Amino-acid content of blood	351	effects of diathermy treatments on	556
Scopolamine comprehensive study of effects of treatment for morphine addiction	194	Thaysen, T L H Blood sugar regulation in idiopathic steatorrhea, origin of low blood sugar curve	477
Seborrhea, idiopathic steatorrhea, regulation of blood sugar in, low blood sugar curve	17	Regulation of blood sugar in idiopathic steatorrhea, the low blood sugar curve	17
Idiopathic steatorrhea blood sugar regulation in, origin of low blood sugar curve	477	Theobromine, effect of purine base diuretics on coronary flow	118
Shifton A L Prolongation of life of nephrectomized dogs with production of edema	424	Theophylline, effect of purine base diuretics on coronary flow	118
Shpiner, L B Blueberry leaf extract overdosage	204	Thompson P K Cerebrospinal fluid in myxedema	368
Sidilek D M Boeck's sarcoid, case with visceral involvement	721	Thompson W O Cerebrospinal fluid in myxedema	368
Silveus, E Cerebrospinal fluid in myxedema	368	Thorax, contour of normal and of tuberculous chests	29
Singleton, A C Rate of evacuation of various foods from normal stomach, preliminary communication	787	Thyroid, toxic adenoma of	73
Sodium chloride effect of, on hypertension	531	Torrance, E G Opium addiction, excretion of morphine by human addicts	862
Somogyi M Rate of glycolysis in erythremia (polycythemia vera)	813	Opium addiction, scopolamine treatment for morphine addiction	194
Spinal Cord, pathologic changes in peripheral nerves and, in diabetes mellitus	576	Opium addiction effects of abrupt withdrawal followed by readministration of morphine in human addicts, with reference to composition of blood, the circulation and the metabolism	1
Sprue and Gee Herter's disease, regulation of blood sugar in idiopathic steatorrhea	17	Opium addiction, effects of intramuscular and intravenous administration of large doses of morphine to human addicts	376
Starch, uncooked, effect of on blood sugar of normal and of diabetic subjects	344	Opium addiction, water balance studies during administration and withdrawal of morphine	693
Steatorrhea See Seborrhea		Torula histolytica, meningo-encephalitis due to	560
Stenstrom W Effects of diathermy treatments on temperature	556	Tuberculosis, contour of normal and of tuberculous chests	29
Sternberg, B Thrombo-angioneurotic changes of kidneys in chronic nephritis	272	of aorta	711
Stewart, S G Eosinophilic hyperleukocytosis in Hodgkin's disease with familial eosinophilic diathesis, report of case and review of literature	772	Undulant Fever presenting clinical syndrome of intermittent hyarthrosis	128
Stomach, influence of diaphragm on esophagus and	856	Urine, chemical study as effected by combinations of ammonium chloride and methenamine	252
Rate of evacuation of various foods from normal stomach	787	fructose in	47
Ulcer See Peptic Ulcer		renal insufficiency associated with Benck-Jones proteinuria, report of 13 cases with note on changes in serum protein	486
Stone, W J Meningo-encephalitis due to torula histolytica	560	treatment of pyuria due to bacillus coli	303
Stowe, W P Intestinal obstruction and septic invasion of peritoneum, combined medical and surgical treatment	543	Veins, hepatic, effect of mechanical constriction of, with reference to coagulation of blood	676
Sturdivant, B F Meningo-encephalitis due to torula histolytica	560	Vos, H Fructosuria	47
Sugar tolerance See Dextrose		Wakefield, E G Inorganic serum sulphates in renal insufficiency, comparative study of blood urea and creatinine, effect of diuresis on serum sulphates	244
Sulphates, inorganic serum, in renal insufficiency	244	Warren, S Pathology of pancreas in non-diabetic persons, study of 156 consecutive autopsies on nondiabetic patients	663
Suprarenals, cortex, and pituitary gland	339	Weight and blood pressure	877
Syphilis of liver, various types with reference to tests for hepatic function	155		



# INDEX TO VOLUME 44

	PAGE		PAGE
Weisman, S A Further observations on contour of normal and of tuberculous chests	29	Wise E C—Continued	
Weiss, S Pneumotachograph in certain intrathoracic diseases its diagnostic value	289	Failure of diabetic patient to utilize dried artichoke powder	362
Westcott, L E Failure of diabetic patient to utilize dried artichoke powder	362	Wolfer, J A Hepatogenic hypoglycemia associated with primary liver cell carcinoma	700
Wiedemer, C Reticulocyte count in normal and in abnormal conditions	209	Wolff, W A Opium addiction, excretion of morphine by human addicts	862
Wilder, R M Diabetes mellitus, pathologic changes in spinal cord and peripheral nerves	576	Woltman H W Diabetes mellitus, pathologic changes in spinal cord and peripheral nerves	576
Wilson, M J Rate of evacuation of various foods from the normal stomach, preliminary communication	787	Wood, F C Hemochromatosis in a metal worker, case report with autopsy and brief review of literature	882
Wise, E C Chemical study of urine as effected by combinations of ammonium chloride and methenamine	252	Woodruff, L W Experimental left and right axis deviation	893
		Ziegler, E E Effect of uncooked starches on blood sugar of normal and of diabetic subjects	344

